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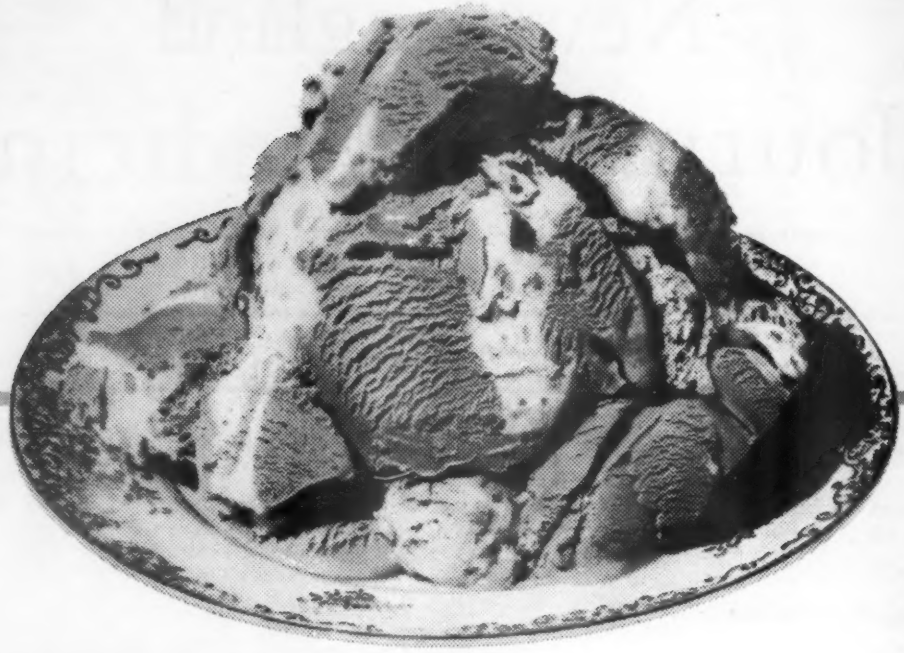

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Volume 237 SEPTEMBER 25, 1947 Number 13

PRESENTATION OF THE HENRY JACOB BIGELOW GOLD MEDAL

INTRODUCTORY REMARKS AND PRESENTATION OF THE MEDAL*

JOE V. MEIGS, M.D.†
BOSTON

THIS evening we meet to do honor to one of our own. Elliott Carr Cutler received his degree in 1913 from Harvard Medical School, where he was a member of the Boylston Medical Society, Alpha Omega Alpha Society and the Aesculapian Club. Thus, characteristically, at the start of his medical career he was a member of the school's literary society, its honor society and its social society. After graduation he went to the Peter Bent Brigham Hospital as surgical house officer. Before the United States entered World War I he was a member of the Harvard Unit, serving with the British Army. On his return to this country he served as resident surgeon at the Massachusetts General Hospital. He then became alumni assistant in surgery at Harvard Medical School and voluntary assistant to the Rockefeller Institute of New York. When the United States entered World War I he joined the Medical Corps of the Army, starting as a lieutenant, but as might have been expected, he was later promoted to captain and then to major. At the end of his military career in the Army, he became resident surgeon at the Peter Bent Brigham Hospital, serving from 1919 to 1921. He subsequently became an associate in surgery at Harvard Medical School. In 1924 he accepted a call to the professorship of surgery at Western Reserve University School of Medicine and was also appointed director of the Surgical Service of the Lakeside Hospital. Here he served with distinction, and one has only to inquire of those who knew him in Cleveland to hear of the great changes and advances that he wrought while there. In 1932, on the retirement of his former chief, the great Dr. Harvey Cushing, he was called back to Harvard Medical School to become Moseley Professor of Surgery and surgeon-in-chief at the Peter Bent Brigham Hospital. It was during that time that he advanced the knowledge of surgery of the heart by his work on the thyroid gland and its relation to heart failure and by the first operation done directly on the valves of the heart to relieve the crippling effects of mitral stenosis. At the Peter Bent Brigham Hospital he produced much original work, but even greater and more lasting than his scientific contributions was his influence on the young surgeons who were so fortunate as to be trained under him. His enthusiasm and his dynamic personality, as well as his profound knowledge of surgery, left their mark on all his students.

In the summer of 1940, immediately after the fall of France, he reorganized Harvard University Base Hospital No. 5. He was farsighted enough to see that in 1940 we had best be prepared. It was natural that with the outbreak of World War II he should have been appointed by the Governor of the Commonwealth as director of the Medical Division of the Massachusetts Committee on Public Safety. Meanwhile, having maintained his connection with the Army as a member of the Medical Officers Reserve, he had been advanced from major to colonel. On July 18, 1942, he was ordered to active duty and immediately became chief surgical consultant, European Theater of Operations. To comment on his accomplishments during that time is unnecessary. All who served under him know what an enormous influence for better surgery he was and how remarkably he improved and aided in the organization of our extremely efficient Medical Service. He was one of the few medical officers who entered for the emergency who was recognized by promotion to the rank of brigadier general.

During his tour of duty in Europe, he visited the medical services in all unoccupied territories and had the great honor of visiting with the Russian Medical Corps. His Army work accomplished, he returned to his old position as Moseley Professor of Surgery, Harvard Medical School, and surgeon-in-chief of the Peter Bent Brigham Hospital.

*This and the succeeding paper comprise the addresses delivered at the presentation of the Henry Jacob Bigelow Gold Medal at a meeting of the Boston Surgical Society, Boston, June 2, 1947. The recipient of the medal, Dr. Elliott C. Cutler, died on August 16, 1947.

†President, Boston Surgical Society.

In 1947 he was appointed acting assistant medical director for the Professional Services Division of the Veterans Administration. His work in this field has been superb. A comparison of the veterans hospitals of today with those of yesterday offers a real idea of the value of this contribution.

He has in his life, as one look at his record shows, done extremely important work in surgery, in research and in teaching. He has found time to belong to a great many civic organizations and may be considered a great public servant. He has been made a member of nearly all surgical associations and clubs and has been honored and decorated not only by his own government but also by those of England, France and Norway. There are few physicians in our time who have done more work, who have taught more delightfully, who have inspired more young men and who — in spite of a full and busy life — have given more time and work to civic pursuits. And few have given more to their country.

Many are the reasons for presenting the Bigelow Medal to Dr. Cutler, the greatest being that he is the embodiment of the many things that most young men aspire to be.

It is an honor to the members of the Boston Surgical Society to present this medal to you, Dr. Cutler.

THE EDUCATION OF THE SURGEON

ELLIOTT C. CUTLER, M.D., Sc.D. (hon.)*

BOSTON

I AM highly sensible of the great honor done me tonight by the Boston Surgical Society through this presentation of the Henry Jacob Bigelow Gold Medal. As one who has attended the presentation of this honor to all previous recipients — ten during the past twenty-five years — and who knows the unusual gifts and attributes of my predecessors, I am overcome with my own inadequacies. Indeed I have done little more in surgery than many of my own age group in Boston. At the same time, I deeply regret that because of difficulties beyond my control, I have been prevented from giving the time and energy to this oration that the occasion richly justifies. Certainly, no greater honor can come to an American surgeon.

I hope that I shall be forgiven if, in introducing my topic, I utilize in part personal experiences that perhaps explain my way of thinking. In fact, the story of my "breaks" with traditional surgical education in Boston is a reason for the very use of my topic, and may have played a larger part in this generous presentation of tonight than is imagined. When I was a medical student, the fourth-year courses were entirely elective, and although a few brave spirits had hidden themselves away in some special laboratory for as long as six months of this last year and, perhaps, in one or two instances for a whole year, this was not considered the proper way to achieve entrance to the better hospital services. During my third year in the medical school, however, I made up my mind that I was to see plenty of surgery in my lifetime and, therefore, should not devote a valuable year to clinical surgery, particularly under the hodgepodge monthly-assignment system then in vogue. Dr. Harvey Cushing, who had already started to guide my errant steps, urged me to put in a year with Dr. Walter Cannon, and although all medical students of my age admired and loved Walter Cannon, as all men did who came to know him throughout his long and productive life, I had come under the influence of Dr. Councilman, professor of pathology at Harvard Medical School, and elected to spend my fourth year with Dr. Frank B. Mallory in his laboratory at the Boston City Hospital. I suspected that many of my teachers, especially the practicing surgeons of Boston, thought that this was a rather foolish enterprise. Yet, as I look back on that precious year, it probably did more for me as a budding young medico than any other year in my lifetime, for with Dr. Mallory I learned the value of precise work and the importance of making and recording correct observations, and I learned to enter the domain of books, for there is time in the life of the laboratory worker to read and study and thus to become aware of the immense amount of knowledge available to the profession. And, finally, I learned some pathology. This is one of the cornerstones of surgery, for if the surgeon cannot tell, let us say, inflammation from tumor in the midst of a perilous abdominal procedure, he can never become a really competent surgeon and is nothing more than a handicraftsman. Moreover, it was this year with Dr. Mallory that led me to spend the next nine months in Krehl's laboratory in Heidelberg, working on a problem that involved pathological disciplines as well as surgery and medicine.

I broke with tradition in this city when I selected the new Peter Bent Brigham for my surgical training. This for me was merely the fulfillment of an ambition to work with Dr. Cushing, who had made,

*Moseley Professor of Surgery, Harvard Medical School; surgeon-in-chief, Peter Bent Brigham Hospital.

early in my medical-school days, an immense personal impression on me. I had already determined to go to Johns Hopkins to work with him after graduation from medical school, only to find that he was coming to Boston. This prevented a change of environment that I had hoped might broaden my medical horizon. After an internship at the Brigham Hospital and a sojourn in a military hospital in Paris, I was most grateful to the Massachusetts General Hospital Staff for accepting me, in 1915, as resident surgeon. There I greatly benefited from the example and opportunity presented to me by the senior members of the West Surgical Service, especially Drs. George W. W. Brewster and C. Allen Porter. This interchange of house staff between the two hospitals was the innovation of a happy custom.

After a year at the Massachusetts General Hospital I again broke with tradition, incurring this time the disapproval of my beloved chief and mentor, Dr. Cushing, by moving to the Rockefeller Institute and studying immunity under Dr. Simon Flexner. I had been offered the privilege of taking over the Hunterian Laboratory at Johns Hopkins by Dr. Halsted, but I came to believe that if I did that I should still be in the environment of clinical colleagues, because so many of the young surgeons there were already friends of mine, and I wished to keep away from the clinic as much as possible so that I could benefit from the stern discipline of a meticulous laboratory worker. I well remember the alarm and even disapproval in the minds of several older surgeons in Boston, who were friends of my family and to whom I had often gone for advice, when I told them I was to study immunity. A leading surgeon of that day asked for information concerning the topic and told me he had never had cause to use such information in his practice!

Then followed World War I and its tremendous experience both in traumatic surgery and in the handling of multitudes of patients. In that war I was privileged to be chief of the professional services in an evacuation hospital and although a lowly captain, taking over from a full colonel in the regular Army, I managed to weather the storm and benefited greatly from the administrative experience of trying to keep a large hospital going all the time, up the line, in the mud, without supplies or much assistance. To be sure, I pilfered liberally from the battlefields, but I rarely complained to headquarters, perhaps because I dared not confront high-ranking people, which left me in the good graces of the chief surgeon of the Theater.

After the war there were further years of training at the Brigham Hospital. Nine years after I had graduated from medical school, I quitted the post of resident surgeon at the Brigham Hospital, becoming a junior member of the staff and spending most of my time in the Surgical Laboratory, studying cardiac surgery. Seen in retrospect, such a bringing up separated me and my ambitions from most of my contemporary colleagues. That I did not know when and where I should settle into an academic life did not seem to bother me at the time, for I was busy and happy in the laboratory. Meanwhile, the Rockefeller full-time plan had just begun, and although it had followed the voluntary full-time arrangement set up by Drs. Christian and Cushing at the Brigham Hospital, it had attracted many followers. I recall long discussions with Dr. Francis W. Peabody and remember that we both believed that there might be certain drawbacks to the Rockefeller system in that the teachers and the men to come under the plan would be robbed of the opportunity to care for their own patients — an important matter, which they were supposed to be able to teach to their students. On this basis I am sure, both Dr. Peabody and I, at that time and later, turned down the Rockefeller full-time system.

The next year, 1923, was a hectic one for me because two medical schools offered me professorships and another discussed the matter with Dr. Cushing and myself, but having taken a look at the candidate, never reappeared. Finally, in 1924, the School of Medicine of Western Reserve University, in Cleveland, made me an offer. The opportunity seemed excellent, and the die was cast. That school, moreover, accepted the so-called "Harvard full-time plan," which was what I desired. No previous clinician had had his office within the walls of the Lakeside Hospital, and when I took over some of the private ward rooms for offices for myself and my young colleagues, it created quite a disturbance. Moreover, I had demanded a good laboratory, and that led the school to more of a financial outlay than perhaps it had anticipated.

The difficulties of transplanting one's self and one's family to a strange city were finally surmounted, although it took several years for the local profession and the populace to realize that the young professor was fit to conduct surgical procedures on men as well as on dogs. It had been rumored about Cleveland before I came that I was an excellent laboratory investigator and knew about the surgery of animals, but had had little experience with man. Even this difficulty, however, had its beneficial side, for it forced me to stick to my laboratory and my wards and to teaching, and to leave the practice to my older colleagues, who were thus made happy and who became eventually my warmest friends and supporters.

Thus, by my early preferences, my training and my first experiences in a clinic of my own, I was directed toward a truly academic life, and tonight I shall speak of the training of the surgeon. Whether or not I have profited by consistently following a course that has for so long been the subject of my thoughts and ambitions, you shall be the judges.

The education of the surgeon really does not begin until he leaves medical school. Yet teachers in graduate schools must consider the early education of the student material handed on to them. It is always to be regretted that in the primary schools little thought is given to the scientific method. All early education is either logic (mathematics) or memory, and memory is the simplest of intellectual functions. And it has seemed a pity that the student's powers of observation and the synthesis of ideas should not have been given some practice. Moreover, postgraduate educators must rely on the medical school for the proper teaching of the medical laboratory disciplines. The surgeons have long decried the diminishing emphasis on anatomy, and now they must worry about the amount of pathology and bacteriology given to their students. Are medical students aware that every operation is an experiment in bacteriology, and are they well grounded in physiology? In my opinion, the medical-school education should be sufficiently broad and sound to allow the student to enter at once into his training as a surgeon. I decry the value of the rotating internship year, now so widely proposed throughout this country, in the education of the surgeon. To my mind, it is merely adding another year to a young man's period of study when he should be getting on with his career. I have long held that the fourth year at the Harvard Medical School is as good as any rotating internship in the country and that students are ready to begin their studies as medical or surgical workers in the broad sense from the moment they leave school. Other Grade A schools are in a similar position. Life is short enough without forcing on the young doctor this additional year, which he cannot well afford; he must some day be prepared to support himself and a family. Moreover, when the student makes up his mind whether he is going into medicine or surgery, — and he can put off a narrower specialty in either of these fields until a later date, — he is wise if he studies the whole hospital plan of the institution where he is to be an intern and is sure that he can acquire there his complete surgical education. This means at least five and usually six years. By that time, he should be fully qualified in the technical art of surgery, should have had enough experience to be proficient in the handicraft side of surgery and, by having been given responsibility as a resident surgeon, should have developed confidence in the practice of his art.

I also wish to emphasize the importance of such an education's being acquired under a single master. Young surgeons who change hospitals frequently never stay long enough to evoke the final interest of the chief surgeon, and since this education is essentially the apprenticeship method, much that is best is lost. It should be pointed out that the education of the physician and that of the surgeon differ essentially in that although many may profit from the medical examination of a patient with a cardiac murmur or some unusual medical sign, only the person who himself conducts the operative procedure can fully benefit from that experience. This handicraft aspect of surgery is something that must be learned, and it must be learned under the most careful tutelage. The young surgeon finally reaches the point where he must be given individual surgical responsibility and the opportunity to operate independently. Only by such practice can he acquire confidence, which is essential to his final development.

The internship should occupy about eighteen months and should be a graduated system in which the beginner progresses from little responsibility to greater responsibility. Thus, he can begin as a worker in the clinical laboratory and finally progress to senior intern on the ward, with perhaps the most junior intern under him, where he is early given the responsibility as a teacher that is a healthy experience. Those who teach are apt to be most thorough, for to teach one must know the subject, which cannot be glossed over before students in the hope that they will assimilate something that has not been told to them. Moreover, this internship year should give him experience not only in general surgery but also in most of the surgical specialties, and the young surgeon must therefore go to a hospital where all aspects of surgery are covered and preferably where they are grouped under the chief surgeon and go into a common internship experience. This year is also rendered more profitable if toward the end of the tour of duty he works in an outpatient department and has the opportunity to care for ambulatory patients who are his direct charge and responsibility and who come back for observation or further study as he directs. While working in the outpatient department he should be under the careful guidance of staff members as well as the residents on his own service, for here he will achieve experience in conducting himself as in his own office practice in the years shortly ahead of him. It is proper to remark that the appointment of an intern is the most important responsibility of the staff of a hospital. If the material chosen is good, there will be a happy house staff and an excellent *esprit de corps*. Moreover, if the interns are competent, the better ones chosen to be assistant residents later on will be of superior caliber, and as the weeding-out process continues, excellence always remains. To draw good interns means close association with medical students, working hard over clinics and all student engagements, and having it generally known that at such and such a hospital the members of the house staff are well treated, carefully guided and always helped when in need. If a hospital is drawing good interns, it usually means that the staff

has been working hard with medical-school responsibilities.

After the internship he should move on to an assistant resident's post, which should occupy about two years and cover periods of four months, at least, in genitourinary surgery, neurologic surgery, orthopedic surgery and gynecology, as well as a major part of his time on the general surgical wards. I hope that while in his major period on the general surgical wards he would have some experience with thoracic surgery, plastic surgery and other less well defined or even narrower surgical specialties. This period as assistant resident should bring the embryo surgeon into close contact with the entire domain of surgical endeavor. It should disclose to him the limitations as well as the possibilities of surgery as a therapeutic agent. His proficiency in the handicraft aspect — what I have called the art of surgery — will greatly increase, and by the end of the period he should be able to perform with safety most of the standard surgical procedures. Such a system for an assistant residency in surgery is again, as with the internship, better if the incumbents begin at intervals of three or four months and then move on into the successive stages of their training as new incumbents arrive. Such a rotation and succession gives to the hospital one man about to complete his service who should be capable enough to substitute for the resident surgeon when he is off duty and thus leave the hospital always well protected. In fact, it is wise to call attention to the fact that any system providing better care of the patients is always the better system — for the pupils, as well as for the patients. Moreover, such a progressive system leaves it incumbent on the senior members of the house staff to teach the newcomers to the service. Here, again, an advantage is achieved both for the patients and for the men in training. A sense of responsibility is developed by this teaching opportunity, and willy-nilly the pupils grow in stature, ability and reliability. After twenty-three years as a professor of surgery, I am convinced that nothing is better for the pupil, as well as his ogre-eyed master, than the steady development of this sense of responsibility. Once it is inculcated in the intern and then polished in the assistant resident it blooms with great vigor and is the major magic in a satisfactory *esprit de corps*.

Having completed his assistant residency, the young surgeon has had three and a half years of sound training in a school for surgery using a common and standardized technic, which is better than if he had served his internship in one hospital, using one technical method, and then moved for his assistant residency to a second hospital where quite a different technic is practiced. Changes of hospital tend to confuse the budding surgeon. He has little knowledge by which to judge which is the better technic and thus may find himself later on practicing a less desirable technic or one that, because he was not deeply enough trained, he does not practice well, with the result that he finds himself a second-rate technician rather than a first-class one. Nevertheless, when the surgeon has put in his three and a half years, the next step should be a year in a laboratory.

This laboratory year is the critical turning point in the career of the young surgeon because, for the first time, he really begins to think independently. Here, medical training has another aspect that differs from surgical training. The surgical interns and assistant residents are apt to be so busy with important, often life-saving, measures that they do more or less what they are told to do and rarely have the time to sit down and think out exactly why they should do a thing or read up on a topic to see that it is proper. The physician, after his morning rounds, does not have to go through three to five grueling hours of physical labor in the operating room applying his therapy, for his therapy has long since been written in the order book. Therefore, with plenty of time to discuss matters, he can sit down and read up on subjects that have been brought up and that he questions. The surgeon is too busy for such relaxation and education, or perhaps he is physically too tired and cannot force himself to hours of study when that is what he needs most. I have long regarded a year in the laboratory as the period that rapidly differentiates growing young surgeons and in which one can soon pick the good, the bad, the indifferent and the exceptional men. The young surgeon, coming from a busy life in which each moment has been dictated by necessity, is often downcast and depressed when put in a laboratory by himself, particularly so if he is left alone and not helped. He feels lost, as if there were nothing to do. But this is the vital point in his career. He must be left alone because he must learn to think for himself. He has been given a problem but does not seem to know how to go about it. It is unwise for even the most generous teacher to help his pupil at that time. Once the young man has learned to think out a problem, stand on his own feet and go to the library and read books, he bursts into his chief's office full of new ideas, and the world is a different place for him. From then on his chief can work with him as much as he wishes in the laboratory, and the two will have great fun together. But the teacher must not do this too early or before the pupil has learned to think and study, lest he injure the pupil's career and his ambitions. It is remarkable how rapidly the young man develops at that time. And at the end of a year that, ten months previously, had seemed so hopeless, he often begs for another year in the laboratory, a request that often cannot be granted because he is needed to become the resident surgeon and to carry on the full responsibilities of running the hospital.

Thus, at the end of four and a half years the surgeon is well trained. He has acquired the technic and the handicraft of surgery, and he has learned how to think. The momentous changes may never be known to anyone but his chief, but the latter will recognize that the change has occurred and that another safe surgeon is ready to carry the torch.

I have spoken as if the product was complete and finished. That is not fully true, although the young surgeon will do well anywhere with the training he has obtained. But this man can be better prepared by being given greater experience and responsibility. This is especially true if he anticipates leading the life of the teacher and investigator in surgery. I pointed out above that only one person receives full benefit from an operative procedure, and that is the surgeon conducting the operation. As an intern, a few simple surgical procedures can be given to the young surgeon under guidance; while he is assistant resident more procedures should be permitted him, and he can safely conduct the simpler ones without assistance but not the greater procedures, which therefore should not be completely relegated to the young surgeon. It is true that the assistant resident surgeon at the end of three and a half years in a good clinic should be so well grounded in the principles of surgery that he can conduct any procedure well. Indeed, in the recent war I watched with delight surgeons only three or four years out of medical school conducting the most complicated thoracoabdominal procedures with complete assurance and great technical polish. A final year in the hospital as resident surgeon will give to the assistant resident surgeon all this assurance and polish and will leave him time to begin to put together his first medical contributions. All teachers should wish to propagate their kind and to leave pupils who can occupy chairs of surgery with distinction. The exceptional man will therefore be chosen by his chief to be the resident surgeon at the hospital. This person represents the attrition of the original young graduates who began together as interns and who saw their first losses when the assistant-resident posts were granted.

The resident surgeon is the head of the house staff. He directs the work of the interns and assistant residents and continuously instructs them; he admits and discharges surgical cases, keeps a watchful eye on the outpatient department and may even advise the laboratory fellow, for all who are not staff members fall under his authority. He is held personally responsible by his chief for the care of all seriously ill patients and must report immediately on all accidents or untoward occurrences on his service. With the visiting staff, he sets the schedule of operations and picks those that he wishes to do. At night he uses his judgment whether to call in a staff member or perform the necessary operation himself. And all the time he is responsible for organizing the undergraduate teaching and for informing staff members of their engagements with students. This is a wide scope of responsibilities, but on its successful performance depends the smooth functioning of the service. After a year or two of such responsibilities, the resident surgeon has absorbed all that a position on the house staff can give him. He may go out to settle in practice or to work up on a senior staff elsewhere, or he may be chosen by his chief to join the senior staff in the hospital where his training began. This resident surgeon represents the finished product in the education of the surgeon. He has been given exceptional experience and great advantages. On his shoulders rests the responsibility for educating another generation of surgeons.

* * *

My story is incomplete, but in handing it on to others I can only hope that they will achieve the happiness that has been mine in the devotion and success of pupils. No way of life can bring greater satisfaction than that which comes to those who enjoy teaching and have the rare privilege of being kept young by disciples. In closing my part of this ceremony I wish to thank the members of the Boston Surgical Society for the great honor that they have this evening given to me.

WEIL'S DISEASE*

A Report of Twenty-Three Cases

E. Craig Heringman, M.D.,† and Jack H. Phillips, M.D.‡

NEW ORLEANS, LOUISIANA

ALTHOUGH Weil's disease is frequently mentioned in various classifications of the causes of jaundice, it has attracted little attention as a condition that can simulate an acute surgical condition of the abdomen. This is not at all surprising because the disease is generally considered to be quite rare in this country. In fact, state and city health departments have only recently become equipped to undertake the proper diagnostic laboratory procedures.

We became interested in this problem during a review of cases of jaundice at Charity Hospital of Louisiana in New Orleans, in which it was found that operations had been performed on 2 patients who subsequently proved to be suffering from Weil's disease. Further investigation revealed that in the six-year period from June, 1939, to June, 1945, a total of 23 cases of Weil's disease were diagnosed and treated correctly. In 1943, Bruno, Wilen and Snavely[1] reported 15 of these cases. Such a large group of cases affords a unique opportunity for the study of this specific infection.

The usual problem in the jaundiced patient is to decide whether the jaundice is obstructive, hemolytic or hepatogenous in origin, and whether operation is indicated. The difficulty in the differentiation of these types of jaundice has been considerably reduced by the newer concepts of liver physiology and bile-pigment metabolism. Steigmann, Popper and Meyer[2] have shown that the correct diagnosis can be made in 95 per cent of patients by careful clinical observation, prolonged study of the urinary excretion of bile pigments and judicious use of liver-function tests.

A case of Weil's disease, however, may turn out to be a diagnostic problem during two separate and well defined stages in the course of the illness. In the incipient or so-called "septicemic phase," the clinical picture can mimic an acute surgical condition of the abdomen so closely that operative intervention is deemed essential. On the other hand, once the second, or icteric, phase of the illness has developed, it must be recognized that the jaundice is not obstructive in character and that surgery is contraindicated. Diagnosis during the second stage of the disease is relatively easy because there is usually sufficient time to study the patient and to determine the results of the various laboratory tests required to establish the true nature of the illness.

*From the Department of Surgery, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana.

†Assistant professor of surgery, Louisiana State University School of Medicine; visiting surgeon, Charity Hospital of Louisiana.

‡Intern, Charity Hospital of Louisiana.

It is evident, therefore, that the greatest difficulty in the correct diagnosis is in the prejaundice phase of Weil's disease, when the symptomatology is variable and misleading. This is borne out by the fact that the only patients in the series who were subjected to surgery were operated on during the early stage of the disease before jaundice was evident. Surgical consultations were requested for 5 additional patients, but in each case jaundice was present and additional laboratory procedures were recommended to establish the diagnosis.

Once these facts became apparent, it was considered worth while to review in detail the 2 operative cases and to discuss the clinical aspects of the other 21 cases to stimulate interest in this disease.

Case 1. E. J. F. (T-40-43067), a 38-year-old housewife, was admitted to the hospital on April 20, 1941, with the complaints of colicky pain in the upper abdomen, nausea and vomiting, a high temperature and backache. These symptoms had begun about 2 days previously, and during the interval severe epistaxis had occurred.

Physical examination revealed a well developed, well nourished woman who appeared acutely ill. No abnormal findings were noted on examination of the heart and lungs. Palpation of the abdomen revealed tenderness in the right upper quadrant. The liver edge was thought to be barely palpable, and voluntary guarding of the abdominal muscles was noted.

The temperature was 104°F., the pulse 116, and the respirations 24. The blood pressure was 128/68.

Examination of the blood disclosed a red-cell count of 4,500,000, with a hemoglobin of 70 per cent, and a white-cell count of 19,600, with 86 per cent neutrophils, 12 per cent lymphocytes and 2 per cent monocytes. The urine had a specific gravity of 1.008 and gave a + test for albumin, but contained no sugar or bile. Microscopical examination of the sediment revealed no cells or casts.

A provisional diagnosis of acute cholecystitis was made. The patient was taken to the operating room on the day of admission, and cholecystectomy was performed. At operation the gall bladder was slightly distended but showed no evidence of inflammation. The liver was moderately enlarged.

During the 1st week after operation the high temperature continued, and the patient suddenly developed marked jaundice. On May 3 the icteric index was 56, and the blood urea nitrogen 36 mg. per 100 cc. Agglutination for *Leptospira icterohaemorrhagiae* reported by the United States Public Health Service was 1:3000 on May 2 and 1:30,000 on May 6. Supportive therapy with 5 per cent dextrose infusions and blood transfusions was promptly instituted. During the third week of illness, the jaundice diminished. An uneventful recovery followed and the patient was discharged on May 20.

The history and physical examination in this case justified the diagnosis of acute cholecystitis. There were practically no early indications of the true nature of the disease except the backache and the possibility that the nosebleed was a manifestation of the hemorrhagic tendency often present in Weil's disease. The temperature of 104°F. was higher

than is ordinarily expected in the usual case of uncomplicated early cholecystitis. When jaundice developed, the possibility of a common-duct stone overlooked at operation was considered. This was ruled out rather promptly, however, by various laboratory tests.

CASE 2. E. G. (I-42-60881), a Negro, was admitted to the hospital on August 30, 1942, with a history of an illness of 3 days' duration. Malaise and anorexia were the primary symptoms, but the patient soon developed pain in the right upper and lower quadrants of the abdomen. Nausea and vomiting occurred frequently during that time, and a cough also developed.

Physical examination disclosed a patient who appeared acutely ill. The heart and lungs were clear to percussion and auscultation. The right side of the abdomen was tender, especially in the right lower quadrant. No rebound tenderness could be elicited, however, and only voluntary rigidity was present. The liver was described as being palpable.

The temperature was 102°F., the pulse 100, and the respirations 25. The blood pressure was 105/60.

Examination of the blood disclosed a red-cell count of 4,300,000, with a hemoglobin of 11.5 gm., and a white-cell count of 12,500, the differential count showing a shift to the left. The urine had a specific gravity of 1.012 and gave a + test for albumin, with no sugar or bile and a trace of urobilinogen. The sediment contained occasional red cells and white cells.

A tentative diagnosis of acute appendicitis was made, and an emergency appendectomy performed. The appendix appeared normal at operation but was removed. Postoperatively, the patient continued to have fever, and on September 3 he became jaundiced. The icteric index rose to 51, and the blood urea nitrogen was reported as 45 mg. per 100 cc. Bile was present in the urine, and occasional granular casts were seen in the sediment on microscopical examination. Agglutinations for *L. icterohaemorrhagiae* were reported as 1:30 but rose to 1:3000 5 days later. Conjunctival hemorrhages appeared, and the patient's general condition grew worse for a few days. The patient was treated symptomatically with blood transfusions and dextrose infusions. Subsequently, the fever subsided, the jaundice cleared, and the patient was able to leave the hospital on September 11.

This patient was examined in routine fashion, and the emergency appendectomy was performed on the basis of the pain in the right side and the elevated white-cell count. There were several factors, however, that might have aroused the suspicions of the examiners. The cough at the onset of the illness, the absence of more signs of peritoneal irritation in the presence of an apparent acute appendicitis of three days' duration and the presence of albumin and cells in the urine were suggestive of a condition other than appendicitis. The difficulty in diagnosis was caused by the fact that jaundice did not appear early, which is true of most cases of Weil's disease.

Since the disease can readily be mistaken for an acute abdominal condition requiring surgery, the clinical aspects should be kept in mind so that it may be suspected early and prompt action taken to establish the diagnosis.

* * *

In 1886 Weil[3] first published his classic description of a specific infectious disease that has since been known as Weil's disease. In his report of 4 cases he was able to describe the condition in detail and to differentiate it from other types of acute jaundice. The illness of his patients was characterized by severe chills, marked prostration, jaundice associated with hepatolienal enlargement, a hemorrhagic tendency and signs of renal failure.

Weil's observations stimulated others to look for this disease, resulting in a marked increase in the number of cases reported in foreign countries. It was not until 1922, however, that Wadsworth[4] published the first account of a proved case of Weil's disease in the United States. From 1922 to 1941 Ashe, Pratt–Thomas and Kumpe[5] were able to collect a total of only 67 reported cases in this country.

Epidemiology

In 1916 Inada[6] found that the etiologic agent was a spirochete that was later classified and named *L. icterohaemorrhagiae* by Noguchi.[7] The usual vector is the adult gray rat, and the rat population serves as a main reservoir for the spirochetes. The majority of cases occur as a result of contamination of the skin by the urinary excretion of infected rats. The organisms can live in a warm damp environment for days and may produce the disease in man by penetration through the nasal mucous membrane,[8] the conjunctivas[9] or abrasions of the skin.[10] The disease is an occupational hazard to miners, sewer workers, fish cleaners and tunnel diggers. Rat elimination is the logical method for the control of the disease. Individual protection by avoidance of water or food likely to be contaminated by the excreta of rats should be practiced. The control problem is understandably difficult, and in New York Weil's disease is now recognized as a compensable disease in fish handlers.

Incidence

Weil's disease has been reported to be rare in children. The youngest patient in this series was thirteen years of age. Twenty of the patients were males, and 4 were females — a ratio of 5:1, as compared to that of 9:1 generally reported in this country. Davidson[11] has demonstrated that the difference in incidence between the sexes is purely occupational.

The reported seasonal incidence during the summer months is adequately illustrated in this series. Most of the cases occurred between April and October, 50 per cent of patients entering the hospital during August and September.

Clinical Features

The incubation period in these cases could not be determined, although it has been reported to average about ten days, with a range of four to nineteen days. The clinical course of the illness may be divided arbitrarily into three stages.

The first or septicemic stage usually lasts from two to five days and is characterized by the presence of spirochetes in the blood stream. The patient complains of an acute onset of nausea and vomiting,

myalgia, prostration, fever and chills. The bradycardia occasionally described was not found in any of the cases reviewed, the pulse rate varying from 110 to 150 per minute. The skin is hot and dry, and petechial hemorrhages may be found anywhere in the body. Abdominal pain is frequently present, although the abdomen is usually found to be soft and scaphoid. Tenderness may be elicited in the right upper quadrant, but there is no evidence of peritoneal irritation. Careful palpation reveals that the tenderness is frequently located in the abdominal wall itself and is probably caused by pathologic changes in the muscles.

The second or toxic stage is ushered in with the onset of jaundice. All but 1 patient in this series became icteric, although world statistics indicate that only half the patients with Weil's disease develop jaundice. Patients without jaundice do not have a second stage but proceed directly into the third or convalescent period.

Jaundice develops most frequently between the fourth and eighth days and is rarely accompanied by pruritus. Evidence of renal damage is also found at about that time. The patient appears extremely ill and may become stuporous, with occasional progression into coma or delirium. The temperature drops from the level of 104 to 106°F. seen in the first stages to 100°F. or even to normal. Signs of bronchopneumonia, with blood-streaked sputum, may be found. The liver becomes enlarged and tender. In 4 cases of this series the spleen was enlarged, although it has been stated by Ashe, Pratt–Thomas and Kumpe[5] that the spleen is usually not palpable.

The convalescent stage is reached after the second week in patients who do not succumb. Kidney and liver function improve slowly after that time, the jaundice recedes, and the fever, which may have persisted into the second stage, subsides. During that period the patient complains only of weakness. Convalescence is complete as a rule in about four to six weeks.

All the patients with Weil's disease whose cases are reviewed were acutely ill on admission to the hospital and had one or more of the manifestations presented in Table 1. The onset of the disease was sudden in 18 cases, and 12 patients remembered the exact hour at which they had become ill.

The laboratory data found in this group of patients were in agreement with those described in the literature. In most cases the white-cell count ranged between 9500 and 24,000. One patient was found to have a leukemic level of 35,000, with a marked shift to the left. The urinary findings in these cases reflected the kidney damage that is present to some degree in all cases of Weil's disease. Albumin, red cells, a lowered specific gravity and a lowered phenolsulfonephthalein excretion were found in practically all cases. The blood urea nitrogen was above 100 mg. per 100 cc. in 10 patients, and in 1 it was 150 mg. The icteric index rose to 300 in 1 case; the average, however, ranged around 76. Cephalin-flocculation, hippuric acid and galactose-tolerance tests, when done, showed evidence of liver damage.

The agglutination titer for *L. icterohaemorrhagiae* was 1:300 or above in the 23 cases reviewed. Tests below 1:300 were not considered diagnostic of Weil's disease. Rising titers occurred in 17 patients and were of value in establishing the diagnosis when there was doubt regarding the etiology of the disease.

Spirochetes were seen on dark-field preparation in only 1 case. The neutral urine or the blood of 4 patients when inoculated into guinea pigs produced findings characteristic of Weil's disease.

TABLE 1. *Symptoms and Signs in Weil's Disease.*

SYMPTOMS AND SIGNS	NO. OF CASES
Fever	23
Headache	17
Muscular aches	17
Jaundice	22
Abdominal pain	15
Vomiting	19
Chills	17
Cough	8
Stiff neck	1
Irrationality	3
Clay-colored stools	3
Palpable liver	18
Palpable spleen	4
Abdominal tenderness	18
Hemorrhagic tendencies:	
Petechiae	3
Conjunctival hemorrhage	6
Gingival hemorrhage	3
Epistaxis	2

Diagnosis

Various provisional diagnoses were made either on admission or after a brief clinical survey before the diagnosis could be confirmed. Weil's disease was considered the most reasonable possibility in 8 cases, acute catarrhal jaundice in 8 cases, acute cholecystitis in 3 cases, bronchopneumonia in 2 cases, appendicitis in 1 case, and typhoid fever in 1 case. A high index of suspicion is evident from the fact that fully 33 per cent of patients were admitted with a tentative diagnosis of Weil's disease, requiring only confirmation by laboratory procedures.

A definitive diagnosis can be made in the first week of the disease by examination of the blood under dark-field illumination or intraperitoneal injection of 5 cc. of the patient's blood into a young, preferably pure-white, guinea pig weighing 175 gm. or less. In the presence of the disease the young pigs become jaundiced and die in from ten to fourteen days. The spirochetes can then be found in the peritoneal fluid of the animal and in various organs.

On dark-field examination the organism appears as an actively motile spirochete from 8 to 15 microns in length and approximately 0.5 micron in width. It is tightly coiled and usually appears as a series

of brightly refractile spots alternately interspersed with nonrefractile areas of the same size. *L. icterohaemorrhagiae* differs from *Treponema pallidum* in that it is more tightly coiled and has a sharp hook at one or both ends, which gives the organism an "S" or "C" shape. Careful study may be necessary to differentiate it from the numerous fibrin particles, which exhibit Brownian movement. Incubation at 27°C. frequently increases the number of organisms in the specimen and aids in their demonstration. Examination of the urine is often of value during the second week, when the organisms are frequently present. Injection of the centrifuged sediment from 60 to 80 cc. of fresh neutral urine diluted with 5 to 10 cc. of physiologic saline solution into the peritoneum of a young guinea pig usually causes the death of the animal at the end of two weeks. Spirochetes can then be seen in the various organs by means of the Levaditi or Giemsa stain.

At about the end of the second week of the illness, antibodies appear in the patient's serum and agglutination tests may be performed. These tests are ordinarily of no value before the ninth day. Strongly false-positive reactions do not occur, and a negative agglutination test after the thirteenth day of illness rules out Weil's disease. High titers may persist for long periods.

Pathology

Post-mortem examination was performed on 2 patients in this series, and pathologic changes were noted primarily in the lungs, kidneys and liver. The lungs showed patchy areas of bronchopneumonia. The kidneys revealed interstitial infiltrations of round cells. The glomeruli were not remarkable but showed some enlargement of the capsular spaces. The tubules were dilated and filled with small amounts of amorphous pink-staining material. The tubular epithelium was swollen and granular. In 1 case Levaditi stains revealed numerous spirochetes within the tubules and in the surrounding stroma. The liver on microscopical examination showed considerable disorganization in the arrangement of the liver cells, which, instead of appearing in continuous cords, occurred in groups of two or three cells. Moderate vacuolization and swelling of the cells were noted. There was no evidence of intrahepatic block. Levaditi stains did not disclose spirochetes in either case.

These findings are in agreement with those described in the literature.[5, 8, 12] Lesions in capillaries and skeletal muscles have been reported frequently. Capillary damage is manifested by numerous small hemorrhages, which can be found almost anywhere in the body, or by severe hemorrhage from any epithelial lined surface that can give rise to symptoms such as melena, hematuria, epistaxis and hemoptysis.

The changes in the muscles have been described as follows by Jeghers et al.[8]:

> There is vacuolization, swelling, loss of cross-striations, hyalinization, infiltration with histiocytes, polymorphonuclear leukocytes and plasma cells, breaking up the substance of the fibers into larger, round lumps of hyalin material, and reabsorption and proliferation of the nuclei of the sarcolemma.

The mechanism of the jaundice in Weil's disease has not been established. Ashe and his associates[5] state that the jaundice is probably due in large part to a true hepatitis. Increased hemolysis or intrahepatic obstruction has also been described by others as a factor in the production of jaundice in Weil's disease.[13]

Treatment

Arsenical drugs have no effect on the spirochetes and are dangerous in the presence of liver and kidney damage. Antimony compounds and sulfonamide drugs are also of no benefit.

Success has been reported in a few cases by treatment with sodium bismuth tartrate.

The therapy of choice at present is the use of penicillin in large dosage and of immune serum. The latter has been used in foreign countries with considerable success but has only recently become available in this country. Up to the present, transfusions of convalescent plasma or blood have been used. Four of the cases reviewed in this series were treated by the latter method and showed a marked response. The rest of the patients were treated by general supportive measures. Penicillin was not available for use in any case.

Mortality

There were 2 fatal cases in this group of 23 patients, a mortality of 8.7 per cent. Ashe, Pratt-Thomas and Kumpe[5] found that the mortality in this country averaged 30 per cent. It is entirely possible that a number of patients in Charity Hospital of Louisiana died in the early stages of the disease before the diagnosis had been suspected, which may account for the relatively low mortality figure in this group.

Summary

Two cases of early Weil's disease subjected to surgical exploration are reviewed in detail.

The clinical features of 21 additional cases are discussed.

Acute surgical abdominal disease and extrahepatic biliary obstruction can both be simulated by Weil's disease, which must therefore be considered in the differential diagnosis.

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CARCINOMA OF THE BREAST

End-Results: Massachusetts General Hospital 1933–1935

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THE present communication is the eighth in a series of reports from the Massachusetts General Hospital dealing with the results following operation for carcinoma of the breast.[1–7] There were 382 cases of carcinoma of the breast during the three-year period, 1933–1935, of which 328 were primary cases and 54 had received earlier treatment elsewhere. Of the former, 92 were inoperable when first seen, and 236 (72 per cent) were submitted to radical operation. Two cases that were untraced are regarded as failures, and 14 cases in which the patients died of intercurrent disease within five years are considered inconclusive. There were 5 postoperative deaths (2 per cent). Although historical data are incomplete, it seems probable that poor initial medical advice accounted for an advanced stage of the disease and consequent failure of cure in 19 patients. In 20 patients the original description of the lesion, with extensive matted axillary involvement, suggested that the operation was ill advised. These patients all succumbed to prompt recurrence, in 17 cases within a year of operation, although all received postoperative x-ray therapy.

In the present series, 40 per cent of patients reported for treatment within two months of the onset of the disease, whereas in 35 per cent the delay was more than six months. In the previous series of cases reported, only 31 per cent delayed over six months after onset. It should also be noted that the operability rate was 80 per cent in the previous series, compared to 72 per cent in the present group. Thus, it cannot be shown that propaganda has succeeded in shortening the time between the first symptom and operation, nor has it caused patients to report in a stage more favorable for cure. On the other hand, the disease was limited to the breast without axillary metastases in 40 per cent of cases, in contrast to 37 per cent in the previous group. This fact, in conjunction with the lessened operability percentage, suggests that criteria of operability have been sharpened. There is still room for improvement in this respect, however, as shown by the 20 cases referred to above in which operation was ill advised.

Preoperative evaluation of axillary lymph-node involvement was erroneous in 19 per cent, generally in the direction of failure to detect involved nodes. This error is considerably less than that in previous series but emphasizes the inaccuracy of clinical appraisal of the extent of disease.

A hundred and twelve patients (50.4 per cent) were living without evidence of disease from five to eight years after operation. Of the cases without axillary involvement, 75.5 per cent were without recurrence after five or more years, whereas of those with axillary involvement the percentage was 33.3. It should be noted that in the latter group are included the 20 cases referred to above. If operation had been withheld from these cases, cures in the cases with axillary involvement would have been 39 per cent, and the operability rate for the entire group would have been 66 per cent. Although axillary involvement is thus obviously of great significance in the prognosis, it should be noted that when only one or two nodes prove to be involved the prognosis is comparable to that in cases without involvement. Specific notation of involvement of only one or two nodes was made in 15 cases, of which 12 (80 per cent) were in the "cured group." It is primarily in the cases with extensive or numerous axillary metastases that the prognosis is poor.

When the patients are divided into three age groups, it is evident that the prognosis is poorest in

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those younger than forty and most favorable in those over sixty years. The poorer prognosis for the younger group is probably due to the fact that this group presents a greater number of cases with higher grades of malignancy and with axillary metastases already established at the time of operation.

The cases of short duration show a definitely greater curability rate than those of longer duration. It should be observed that the lesions of a high grade of malignancy that are operable are usually of short duration. Hence, the group of short duration always contains a disproportionately large number of extremely malignant lesions, in which the prognosis is poor. The cures in such lesions are predominantly in the group of short duration and it is only in this group that a considerable number with this type of lesion are cured even when the nodes are involved.

The gross characteristics of the primary carcinoma, especially its size, are significant in the prognosis. Thus, five-year survivals were obtained in 89 per cent of cases with lesions less than 2 cm. in greatest diameter, in contrast to 18 per cent if the lesions were greater than 4 cm. in diameter. The same disparity obtains when cases with or without lymph-node involvement are contrasted. The larger the primary lesion, the greater the incidence of involvement.

The lesions were grouped into three grades of malignancy, according to Greenough's criteria. There were only 11 cases in the lowest grade. None of these presented axillary lymph-node involvement, and cure resulted in all cases. Axillary nodes were involved in 60 per cent of cases with Grade II lesions, and in 65 per cent of the lesions of highest grade. Cure was achieved in 59 per cent of cases with Grade II lesions, including 86 per cent of those without and 40 per cent of those with lymph-node involvement. Cure was obtained in 38 per cent of cases with Grade III lesions, including 57 per cent of those without and 27 per cent of those with nodes. It is obvious that the cases of high malignancy have a poorer prognosis when cases of comparable extent are considered, and it is also evident that a high proportion of these patients present axillary metastases when first seen. Another finding of significance is that local recurrence took place in 18 per cent of cases with Grade III lesions, in contrast to 7.6 per cent of those with Grade II lesions.

Biopsy and immediate pathological examination were performed in 116 cases. Fifty-five of these patients proved to have axillary involvement already present, which suggests that biopsy was resorted to in many cases when the diagnosis was probably clinically obvious. Although the over-all results in the biopsied group show 57 per cent five-year survivals, this favorable showing is doubtless due to the inclusion of a large proportion of the early and doubtful cases. That the procedure is not entirely free from hazard is shown in the fact that recurrence in the operative field occurred in 15 per cent of the biopsied group, in contrast to 7.5 per cent in the cases not submitted to biopsy.

Recurrences in the operative field may constitute a reflection on the care with which cases are selected for operation and on the operative technic. There was such recurrence in 11 per cent of the present group. As noted above the rate was highest in cases with a high grade of malignancy and also in cases submitted to immediate pathological examination. It is also noteworthy that there is an increased likelihood of operative-field recurrence when the primary carcinoma is large and when axillary metastases are present. Although these findings are not conclusive, they suggest that the extent and character of the primary carcinoma have greater significance than the operative technic.

X-ray therapy has been used as the treatment of choice in inoperable cases and in the treatment of recurrences. Preoperative x-ray therapy has not been employed. Postoperative x-ray therapy was used in a certain number of cases in which the surgeon believed that he had left gross carcinoma after operation, and in some others in which clinical and pathological features augured a poor prognosis. It was not employed routinely in the present series, and it is not demonstrable that any benefit was obtained in the cases in which it was used prophylactically.

Summary

This report is the eighth in a series of end-result studies of carcinoma of the breast treated at the Massachusetts General Hospital.

Survivals of five to eight years without recurrence were obtained in 75.5 per cent of cases without axillary lymph-node involvement, in 33.3 per cent of those with axillary metastases and in 50.4 per cent of the entire group submitted to radical operation.

Improvement in curability, as compared with that in previous series of cases, may have been due to better selection of cases suitable for operation, as well as to improved operative technic. Benefits due to shortening of the preoperative duration as a result of educational campaigns were not conspicuous in this series. The occasional employment of postoperative prophylactic radiation does not appear to improve the prognosis.

The presence or absence of axillary lymph-node metastases is of marked significance in the prognosis. Other important factors are the size and duration of the primary lesion, the grade of malignancy and the age of the patient. These factors not only affect the prognosis but also have a bearing on the incidence of operative-field recurrence.

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PLASMA-VOLUME DETERMINATIONS IN RHEUMATIC SUBJECTS DURING ORAL SALICYLATE THERAPY*

Report of a Case with Severe Hemorrhage

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COBURN'S[1] report advocating large doses of salicylates in rheumatic fever aroused widespread interest in the problem of salicylate intoxication. The milder symptoms of nausea, vomiting, tinnitus, deafness and vertigo are considered to be of minor significance. The origin of these symptoms and the action of sodium bicarbonate in alleviating them have been discussed by Smull and her associates[2] and Caravati and Cosgrove.[3] The more serious toxic complications, including death, delirium, dyspnea, acidosis, hypoprothrombinemia and hemorrhage have been investigated by Ryder et al.,[4] Manchester,[5] Owen and Bradford[6] and Jager and Alway.[7] The last investigators suggested the possibility of an increased plasma volume during intensive salicylate therapy because of changes noted in the hematocrit and plasma proteins and by determination of the plasma volume by the dye method in some cases.

Accordingly, 7 rheumatic patients receiving large oral doses of sodium salicylate were studied for changes in the plasma volume.

Materials and Methods

Of the patients studied 6 had rheumatic fever, and 1 had rheumatoid arthritis. The plasma volume, hematocrit and plasma protein concentration, prothrombin activity and salicylate concentration were determined on admission. The patients were then given sodium salicylate orally without sodium bicarbonate in a dosage such that plasma salicylate concentrations of not less than 35 mg. per 100 cc. were expected.

Plasma volumes were determined by the ten-minute-sample method of Gregersen[8] and Noble and Gregersen,[9] as modified to the use of the Cenco photelometer. A calibrated syringe was used for the injection of the dye T–1824.§ Duplicate venous hematocrits determined in Wintrobe tubes and plasma protein determinations by the method of Bowman[10] were done on the control and dye samples. The prothrombin time was determined by a modification of the Quick[11] method using thromboplastin prepared from the human brain. The prothrombin activity as a percentage was obtained by comparison with diluted normal human plasmas. Plasma salicylate concentrations were determined by a modification of the method described by Coburn.[1]

The plasma volume, hematocrit and plasma protein concentration, prothrombin activity and salicylate concentration, which were determined at frequent intervals during therapy, are presented, with other relevant data, in Table 1.

Results

An increase in the plasma volume was noted within ten days after the beginning of oral salicylate therapy in 5 of the patients in this study. Changes in the plasma volume are better expressed as percentage change, in that the actual volume varies with the weight and size of the patient. The increases noted were 38 per cent (1450 cc.) in Case 1, 6.5 per cent (210 cc.) in Case 3, 16 per cent (550 cc.) in Case 5, 14 per cent (275 cc.) in Case 6 and 11 per cent (340 cc.) in Case 7. A decrease in plasma volume occurred in 2 cases, being 9.6 per cent (240 cc.) in Case 2 and 4.0 per cent (80 cc.) in Case 4.

In 8 convalescent patients with no evidence of cardiovascular disease, a series of thirty-four control determinations of plasma volume by the method used in this study showed variations from +4.3 to —6.9 per cent.

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§Kindly supplied by the Warner Institute of Therapeutic Research, New York City.

The greatest increases in plasma volumes occurred in patients with pre-existing valvular disease who were experiencing salicylate toxicity. Cases 1 and 5 showed evidences of salicylate intoxication by anxiety, severe tinnitus, gross tremor, acidosis (acetonuria and lowered carbon dioxide combining power), lowered prothrombin activity and pulmonary congestion (basal rales) at the time the second plasma volume was determined. In Case 6 the same symptoms and signs were demonstrated, but the carbon dioxide combining power was not measured. One patient (Case 3) never had more than mild symptoms of intoxication.

Decreased plasma volumes occurred in Cases 2 and 4. In the former the salicylate concentration in the blood never exceeded 22 mg. per 100 cc., owing to poor co-operation on the part of the patient necessitating lower dosages. In the latter there was blood loss, and twenty-four hours after the second plasma-volume determination, clinical shock was evident.

After prolonged sodium salicylate therapy 6 patients showed plasma volumes that were increased from the initial values. The average increase was 9 per cent. One patient (Case 3), who was treated in an original monocyclic attack of acute rheumatic fever and who showed an increase of 6.5 per cent in plasma volume after a week of intensive oral salicylate therapy, had a return of the plasma volume to the original level while continuing the salicylate. When rechecked two weeks after the last dose of drug a plasma volume 6 per cent less than that on

TABLE 1. *Plasma-Volume Determinations and Other Pertinent Data.*

Case No.	Age	Sex	Diagnosis	Date	Plasma Volume	Change	Hematocrit (Wintrobe Method)	Plasma Protein	Salicylate Dose	Plasma Salicylate Concentration	Prothrombin Activity
	yr.				*cc.*	*%*	*%*	*gm./100 cc.*	*gm.*	*mg./100 cc.*	*% of Normal*
1	18	M	Aortic and mitral insufficiency and mitral stenosis (functional, Grade III*)	5/25	3760	—	47.3	5.9	0.0	0	Less than 10
				5/27	—	—	—	—	8.5	31	37
				5/29	—	—	—	—	8.5	51	22
				5/31	—	—	—	—	8.5	47	20
				6/3	5210	+38.0	45.9	5.9	8.5	51	Less than 10
				6/6	—	—	—	—	4.3	41	43
				6/10	—	—	—	—	4.3	12	45
				6/15	4020	+7.0	40.7	5.7	4.3	15	70
				6/20	—	—	41.5	—	4.3	14	49
				7/6	—	—	—	—	6.0	21	75
				7/9	—	—	—	—	6.0	26	70
				7/12	—	—	—	—	4.0	19	46
2	13	M	Aortic and mitral insufficiency (functional, Grade II*)	7/8	2480	—	32.6	4.5	10.0	18	60
				7/10	—	—	—	—	10.0	—	34
				7/12	2240	−9.6	30.0	4.8	6.0	64	12
				7/13	—	—	—	—	3.0	—	Less than 10
				7/14	—	—	—	—	0.0	23	33
				7/15	—	—	—	—	0.0	0	60
				7/19	—	—	—	—	4.0	13	80
				7/24	—	—	—	—	4.0	17	90
				7/29	2690	+8.5	37.7	6.0	4.0	0	—
3	15	M	Mitral insufficiency (functional, Grade I*)	6/26	3210	—	42.3	7.4	0.0	—	60
				7/1	—	—	—	—	10.0	13	—
				7/3	3420	+6.5	40.3	7.0	10.0	—	27
				7/5	—	—	—	—	10.0	42	28
				7/9	3120	−2.8	41.7	7.7	10.0	48	24
				8/2	—	—	43.0	7.0	0.0	—	—
				8/5	3010	−6.2	43.2	7.8	0.0	—	80
4	15	F	Mitral insufficiency (functional Grade I*)	6/7	2240	—	38.6	7.8	4.0	3	95
				6/12	—	—	—	—	5.5	11	100
				6/18	2160	−4.0	37.9	7.3	5.5	22	80
				6/27	2500	+11.5	38.4	8.4	0.0	0	100
5	44	M	Rheumatoid arthritis	4/18	3210	—	47.1	5.4	0.0	0	20
				4/23	3420	+6.5	44.7	5.1	12.0	29	—
				4/24	—	—	—	—	16.0	38	—
				4/27	3760	+16.1	40.1	4.8	13.0	37	38
				4/29	—	—	—	—	0.0	6	100
				5/1	3760	+16.1	39.8	4.9	3.0	—	—
				5/14	—	—	—	—	10.0	17	100
				5/22	—	—	—	—	9.0	—	95
				5/28	—	—	—	—	9.0	—	90
				6/1	—	—	—	—	9.0	13	—
				6/8	—	—	—	—	4.0	—	80
				6/20	3330	+3.7	39.9	4.5	4.0	—	65
6	16	F	Mitral stenosis and insufficiency (functional, Grade II*)	5/1	1935	—	39.5	8.0	0.0	0	100
				5/4	—	—	—	—	12.0	46	—
				5/6	2210	+14.0	35.6	7.4	12.0	57	Less than 10
				5/7	—	—	—	—	0.0	32	50
				5/8	—	—	—	—	0.0	—	60
				5/10	—	—	—	—	0.0	3	100
				5/15	2320	+19.0	34.7	7.0	0.0	0	—
				6/19	2210	+14.0	31.0	6.9	0.0	0	—
7	14	F	Mitral stenosis and insufficiency (functional, Grade III*)	7/25	—	—	—	—	1.3	0	85
				8/2	2160	—	41.3	6.8	5.0	17	70
				8/5	—	—	—	—	5.0	29	48
				8/9	2500	+11.1	39.8	6.9	5.0	30	50
				8/16	—	—	—	—	8.0	48	65
				8/23	2320	+7.4	39.8	6.7	6.4	45	57
				8/29	—	—	—	—	6.4	47	31
				9/6	—	—	—	—	6.4	33	39
				9/13	2210	+2.3	43.9	—	6.4	37	55

*Functional capacity based on criteria outlined by the Criteria Committee of the New York Heart Association.[11]

admission was found. In the remaining 5 cases, once the increase had occurred, the plasma volume remained at an elevated level even after all medication had been omitted, and only slowly returned toward the initial value.

From our data it is evident that the hematocrit and plasma protein determinations did not consistently reflect the changes in plasma volume as measured by the dye method.

Changes in the prothrombin activity in 6 patients followed a rather irregular pattern. In the main, however, whenever a plasma salicylate concentration of over 35 mg. per 100 cc. was present, there was a definite and persistent depression of the prothrombin activity. Hemorrhagic episodes were not observed in any case except in Case 2. One patient (Case 1) had a prothrombin activity of 0 on admission, but it could not be established whether or not salicylates had been administered before admission. Another patient (Case 2), whose prothrombin activity had progressively decreased while he was receiving massive doses of salicylate therapy orally, developed severe intoxication and hemorrhage. This case is reported in detail below.

Case Report

D. V., a 13-year-old boy, was admitted to the hospital with a history of repeated episodes of nasal bleeding and painful swelling of the joints of brief duration. He had had rheumatic fever 3 years previously, when he had been treated with prolonged bed rest; he had subsequently been limited in school athletics because of a heart murmur.

Physical examination revealed a well developed and well nourished boy, who appeared ill and obviously favored the left knee. There was mild injection of the pharynx. The lungs were clear. The apical impulse was heaving and palpable in the fifth left interspace in the midclavicular line. The left border of cardiac dullness fell at the same point. The rhythm was regular, and the rate rapid. There was a soft, blowing systolic murmur at the apex and harsh systolic and blowing diastolic murmurs at the base and along the left sternal border. The abdomen was soft and nontender, and the liver and spleen were not palpable. The left knee and, to a lesser degree, both ankles were red, hot, tender and swollen.

The temperature was 102°F., and the pulse 120; the blood pressure was 120/60.

The patient had obviously received salicylates before admission, since the blood salicylate concentration was 15 mg. per 100 cc. and the prothrombin activity was 60 per cent. He was given 10 gm. of sodium salicylate daily by mouth. A prompt clinical response occurred within 24 hours. This dosage was continued for 4 days, when nausea and anorexia, anxiety, a gross tremor, flushing and sweating, an increased respiratory rate without dyspnea and a few fine rales at the right base first appeared. The carbon dioxide combining power was 40 vol. per cent, and a urinalysis was negative except for a + test for acetone. The plasma salicylate concentration was 64 mg. per 100 cc., and the prothrombin activity 12 per cent of normal.

On that day of treatment bleeding from the nose was first noted but did not appear to be severe, since the amount of blood was small and examinations of the posterior pharynx did not suggest that any great amount of blood was being lost by this route. During the afternoon the patient vomited once, and there was no gross blood in the vomitus. Vomiting recurred on the following morning, its appearance suggesting old blood to the nurse, but the specimen was discarded. Throughout the 5th day there was intermittent nasal bleeding, and 6 gm. of sodium salicylate was given. A plasma-volume determination was 9.6 per cent (240 cc.) less than that on admission. The nasal bleeding continued during the night. On the following day, the patient appeared listless and pale and complained of nausea and malaise. Salicylates were omitted. During the early evening the patient fainted in bed. He immediately regained consciousness, and examination revealed no evidence of nasal bleeding at that time. The blood pressure was 110/45. Shortly thereafter the patient vomited 600 cc. of bright-red, loosely clotted blood. An hour later a similar amount was vomited, and the blood pressure was 94/40. The prothrombin activity at that time was reported as less than 10 per cent. The patient was immediately given molar sodium lactate and 64 mg. of menadione bisulfite intravenously, as well as 500 cc. of fresh whole blood. A third vomiting of 500 cc. of bright-red blood occurred before transfusion. Two hours after the transfusion the blood pressure was 120/40; no further evidence of bleeding occurred. Further transfusions were given on the following 2 days. On the 3rd day after the last dose of salicylate, the plasma salicylate concentration was 0, and the prothrombin activity was 60 per cent of normal. The patient was asymptomatic at that time. Twenty-four hours later the temperature reached 103°F., and he complained of abdominal pain, dryness of the throat and a desire to cough. The chest was clear, but the abdomen was diffusely tender with rebound tenderness but no localizing signs. Sodium salicylate was resumed with a daily dose of 4 gm. orally, and the administration of 25,000 units of penicillin every 3 hours prophylactically was begun. A prompt amelioration of symptoms resulted. Penicillin was continued for 8 days, and the salicylates were increased to 5 gm. daily. The prothrombin activity remained within normal limits. Thereafter, convalescence was uneventful. A plasma-volume determined 16 days after the hematemesis and transfusions was increased 8.5 per cent (450 cc.) over the initial volume. The plasma salicylate at that time was 17 mg. per 100 cc.

Discussion

From this study of 7 patients who received oral sodium salicylate therapy it is evident that the plasma volume tends to increase at some point during the course of treatment. A possible explanation for this may be found in the study of Lyons, Jacobson and Avery,[13] who demonstrated a significant increase in the plasma volume in 14 normal subjects who received large amounts of sodium chloride or sodium bicarbonate by mouth. It is our hypothesis that with large doses of sodium salicylate enough sodium may be ingested to result in a measurable increase in the plasma volume. In patients receiving both sodium salicylate and sodium bicarbonate such an effect would be even more reasonable.

In Case 1 a prompt increase in the plasma volume of 38 per cent was noted. This increase was coincidental not only with signs of salicylate toxicity but also with clinical evidence of increasing heart failure. This patient, with pre-existing aortic and mitral valvular disease and a recurrence of acute rheumatic fever, was admitted in mild chronic congestive failure. He showed an initial high plasma volume. This is consistent with the reports of Gibson and Evans,[14] Seymour et al.[15] and Warren and Stead.[16] In such cases the addition of more sodium ions through the medium of sodium salicylate therapy may have been the basis for a further increase in plasma volume and a coincident increase in heart failure.

Summary

Definite increases in plasma volume occurred in 6 of 7 patients studied during oral sodium salicylate therapy.

The degree of prior valvular damage, together with the acute disease and the added sodium ions of the drug, appear to be the factors responsible for the increase in plasma volume.

When plasma salicylate concentrations were maintained in the range of 35 mg. per 100 cc., an associated depression of prothrombin activity was found.

One case is presented in detail because of the occurrence of a severe hemorrhage, associated with a marked hypoprothrombinemia.

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MEDICAL PROGRESS

HEMATOLOGY (Concluded)*

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BOSTON

Hemorrhagic Diseases

As previously stated the hemorrhagic diseases may be classified as those due to a defect, usually a reduction, in the blood platelets, to a defect in the coagulation factors of the blood and to a disturbance of the capillaries.[91]

Thrombocytopenic Disorders

Qualitative abnormalities of the platelets undoubtedly exist, but they are exceedingly rare as compared with quantitative changes. Marked reductions in blood platelets (thrombocytopenia) occur in a number of conditions and may be due to bone-marrow disease, such as hypoplasia, aplasia, leukemia or other infiltration; deficiency of liver-extract principle (pernicious anemia), iron or certain components of the vitamin B complex including folic acid; to the hypersplenism of splenomegaly that is caused by cirrhosis of the liver, chronic infectious splenomegaly, disorders of lipid cellular metabolism and other conditions; allergic reactions to drugs and foods; various conditions, usually infectious diseases but with the bone-marrow picture as seen in the idiopathic group mentioned below; and unknown disorders usually associated with the "hypersplenism" of an abnormal spleen and generally requiring removal (idiopathic thrombocytopenia).

In thrombocytopenia due to actual disease of the bone marrow, whether hypoplasia, aplasia, leukemia or neoplastic infiltration, the sternal-puncture aspiration of the marrow shows great diminution or complete lack of megakaryocytes. In idiopathic thrombocytopenia megakaryocytes are numerous. Thus, a simple puncture-aspiration biopsy of the sternal marrow is of great value in differentiating the two types of disturbance.

Thrombocytopenic purpura as a complication of an acute infectious or exanthematous disease is fairly common. This is particularly true of children. Kaufman[92] reports the cases of 2 children who developed thrombocytopenic purpura after scarlet fever. The second case showed 8 per cent eosinophils in the blood. Unfortunately, sternal-marrow examinations were not done. Methionine and foods high

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in this amino acid were used for treatment with prompt cessation or diminution in the hemorrhagic tendency. Further trial with this therapeutic method is desirable. Two cases of German measles complicated by thrombocytopenic purpura are reported by Warren, Rogliand and Potsubay.[93] Uneventful recovery ensued in both, as it almost always does in cases associated with an acute infection. In a case of infectious lymphadenosis (mononucleosis) presented by Dameshek and Grassi,[94] however, the thrombocytopenia and bleeding were so marked that splenectomy had to be resorted to and was followed by dramatic recovery. It was thought that the large spleen that was present was contributing to the development of marked "hypersplenism" and thus to the thrombocytopenia. Thrombocytopenia occurring in the course of malaria is reported by Schrager and Kean.[95] This is extraordinarily rare, occurring perhaps once in 10,000 cases of the disease.

Boeck's sarcoid with thrombocytopenic purpura is reported by Enzer[96] and by Nordland et al.[97] In Enzer's case there was generalized sarcoidosis with splenomegaly and pancytopenia. Splenectomy was followed by uncontrollable hemorrhage, which led to death. On the other hand, I have seen cases of Boeck's sarcoid of the spleen in which splenectomy led to a complete recovery in the platelet level and cessation of bleeding. Nordland and his associates[97] observed a similar case in which what appeared to be typical fulminating idiopathic thrombocytopenic purpura developed during the fifth month of pregnancy. Splenomegaly was present, however, and was difficult to explain, since in the idiopathic disease the spleen is hardly ever enlarged. The spleen was removed and showed Boeck's sarcoid, and the patient made an uneventful recovery. The author discusses 13 cases of idiopathic thrombocytopenic purpura, 7 with splenectomy during pregnancy. Patterson[98] reports a case of idiopathic purpura occurring during pregnancy in a twenty-two-year-old primipara with a strong family history of hemorrhagic disease. Bleeding manifestations began during the fifth month of pregnancy, and postpartum bleeding was excessive. The newborn infant developed purpura and bleeding in the stools and showed a platelet level of 18,000. Both the mother and the infant subsequently recovered. This case is worthy of comment for several reasons: the occurrence of thrombopenic purpura in the infant of a thrombopenic mother indicates the possibility of a circulating antiplatelet growth factor, which is consistent with the conception, expressed below, of a splenic factor that enters the blood stream and causes inhibition of megakaryocytes; and the question is open whether conservative treatment was justified in this case even though it worked out happily, since the mother might have bled uncontrollably at delivery. Had splenectomy been performed at the fifth month, the baby would not have developed thrombocytopenia, and the maternal bleeding would have been minimal at delivery.

Some cases of the hypersplenism caused by splenomegaly continue to be reported as idiopathic thrombocytopenic purpura. Splenomegaly is often associated with leukopenia, neutropenia, thrombocytopenia and anemia.[91] There is either pancytopenia or a selective cytopenia or group of cytopenias. The splenomegaly may be due, as noted above, to Boeck's sarcoid, chronic infections of the spleen, cirrhosis of the liver, splenic-vein thrombosis, Gaucher's disease or unknown causes. Splenectomy usually brings the blood picture back to normal whatever the underlying condition. Suchecki and Glass[99] report the case of a Nigerian Negro with a large spleen in whom marked hemorrhagic manifestations (diagnosed as idiopathic thrombocytopenic purpura) were present. The blood showed pancytopenia. Splenectomy was followed by a dramatic response.

Dameshek and Miller[100] discuss the sternal-marrow findings with particular reference to the megakaryocytes in idiopathic thrombocytopenic purpura, which they regard as a form of hypersplenism. The blood in this condition is characterized by an extreme reduction in platelets. Paradoxically, however, the platelet precursors in the marrow — that is, the megakaryocytes — are increased. Careful histologic study of the megakaryocytes demonstrated a greatly diminished platelet production. After splenectomy platelet production became extraordinarily marked, indicating that before splenectomy something had been inhibiting platelet production from megakaryocytes. Since splenectomy resulted in correction of this defect, the spleen was suspected of being the site of an abnormal material or an abnormal amount of normal material causing megakaryocytic inhibition. The disorder was thus thought to be a form of hypersplenism with enlargement of the spleen. The diagnostic value of the sternal-puncture test in the differentiation of idiopathic and other forms of purpura is discussed.

Schwartz[101] reports the bone-marrow findings in idiopathic thrombopenic purpura, with particular reference to the concentration of eosinophils and their diagnostic and prognostic significance. He observed that when more than 50 eosinophils were found per 1000 granulocytes the patient usually made a spontaneous recovery without splenectomy. These cases were thought to be of allergic nature. There can be no question that an allergic reaction — whether to an infection, drug or food — results in a megakaryocytic reaction, with a reduction in platelets. Schwartz's contention that the finding of marrow eosinophils is definitely indicative of such a reaction cannot yet be definitely proved.

Aggeler, Howard and Lucia[102] discuss their data on platelet counts as related to bleeding time, coagulation time, capillary fragility and degree of

clot retraction in 64 normal subjects and in 404 patients suffering from various diseases. The counts are of distinct value if done by the same person day after day. Parenthetically, it may be said that platelet counts performed only occasionally are best not done at all, since they are subject to great inaccuracy. Estimation of the number of platelets on a well spread cover-slip smear is much better than the occasionally performed platelet count. Aggeler et al. found a statistically significant relation between the platelet count, the bleeding time and the clot retraction. In the stage of recovery from idiopathic thrombocytopenic purpura there may be some dissociation between these factors.

A peculiar type of thrombopenic purpura associated with hemolytic anemia and generalized platelet thrombosis is described by Trobaugh and his associates.[103] Death occurred two weeks after the onset of illness. At autopsy widespread platelet thrombi were present in small blood vessels throughout the body. About 15 similar cases have already been recorded. Graña[104, 105] reports the experimental production of thrombopenic purpura in dogs and guinea pigs by the injection of heterophil antibody of the Forssman type. Not only was the platelet count depressed but also the capillary walls showed evidence of injury. This paper points to the possibility of an abnormal agglutinating mechanism in the pathogenesis of some cases of idiopathic thrombocytopenic purpura. Skelton and his co-workers[106] found that alpha tocopherol (vitamin E) prevented or cured the picture of experimental thrombocytopenic purpura of antiplatelet serum. This material was apparently used with beneficial results (although detailed statements are not made) in 5 cases of idiopathic thrombocytopenic purpura and in 5 cases of other types of purpura. This form of therapy requires further study.

A case of thrombocytopenic purpura due to potassium iodide administration is reported by Davis and Saunders.[107] Discontinuance of the drug resulted in subsidence of the purpura, and experimental reproduction was achieved later by a single administration of 0.5 gm. The development of purpura during heat stroke was studied by Wright, Reppert and Cuttino.[108] The hemorrhagic disturbance was apparently the end result of both thrombocytopenia and a decrease in prothrombin concentration of the blood, the latter being due probably to extensive hepatic damage. Bone-marrow smears revealed no abnormalities of the megakaryocytes.

Defects in Coagulation Factors

Hypoprothrombinemia. The most frequent coagulation defect is that involving prothrombin. Quick[109, 110] emphasizes repeatedly that his original methods for the preparation of thromboplastin and for performing the prothrombin test have been considerably modified, leading in many cases to inaccurate results. Aggeler and his associates[111] present a critical analysis of the Quick test for prothrombin and conclude that the use of a single specimen of blood from one normal subject as a normal standard may lead to considerable error. To establish reliable normal standards, the blood of at least 5 normal subjects should be individually tested with the same specimen of thromboplastin, and the results averaged. It is suggested that a carefully prepared and stored dehydrated human brain is a more potent source of thromboplastin than the average rabbit brain.

The development of hypoprothrombinemia during salicylate therapy appears to be a definite phenomenon. Govan[112] reports his studies of 24 children receiving salicylates, mostly aspirin. In 6 cases an abnormal prolongation of the prothrombin time occurred. The most marked changes occurred between the second and fifth days of medication. Despite continuation of salicylates, the prothrombin time returned to normal values by the ninth day. Owen and Bradford[113] studied 25 adults with rheumatic fever who received 10 gm. of salicylates intravenously daily. The prothrombin levels fell to 10 to 59 per cent of normal within one to six weeks. Bleeding in the form of epistaxis or splinter hemorrhages occurred in 5 cases at the time of maximum prothrombin depression. Clausen and Jager[114] attempted to correlate the degree of hypoprothrombinemia with plasma salicylate levels rather than with the total daily dose. A direct correlation was found in both human beings and animals between the height of the plasma salicylate level and the degree of hypoprothrombinemia. Significant reductions in the prothrombin level (to 40 per cent of normal) did not occur until plasma salicylate levels of at least 600 microgm. per 100 cc. were reached, varying doses of salicylates being required for this purpose.

Prolongation of the prothrombin time by quinine was reported by Pirk and Engelberg.[115] Quick[116] studied this matter further and found no such prolongation. He also showed that the administration of vitamin K in large doses did not cause a hyperprothrombinemia. In this article Quick attempts to discredit further use of the term "hypoprothrombinemia."

A diminution in circulating prothrombin (increased prothrombin time, hypoprothrombinemia) occurs not only in obstructive jaundice and hepatitis but also in severe dietary inadequacy, in chronic diarrhea and in pregnancy. Rapoport and Dodd[117] report 7 cases of hypoprothrombinemia in infants with prolonged diarrhea. The hemorrhagic manifestations and the prothrombin levels were adequately controlled by the parenteral administration of vitamin K.

Meyers and Poindexter[118] studied the prothrombin levels in patients with both occlusive coronary disease and angina pectoris. Coronary occlusion

produced a definite shortening of the prothrombin time within twenty-four to seventy-two hours after the beginning of the attack and lasting for several weeks. This abnormality may be due to a release of excess thromboplastin from injured heart muscle and perhaps by disintegration of platelets in the mural thrombus.

Ogura et al.[119] studied 27 cases of coronary occlusion by the Waugh–Ruddick test and demonstrated accelerated prothrombin time in 78 per cent of cases. This occurred beginning with the second or third day and continued until the seventeenth day. The technic of the Waugh–Ruddick test is described in the article. Cotlove and Vorzimer[120] observed the prothrombin time in 76 cardiac patients and found that no alterations in this test occurred in either coronary occlusion or angina pectoris. (These contradictory findings have no particular bearing on the use of dicoumarol for the treatment of coronary thrombosis, as suggested by Wright and his associates.[108] Whether the use of dicoumarol represents good medical practice is not yet completely certain.)

Scherf and Schlachman[121] studied the prothrombin time in 22 cardiac patients receiving methylxanthines such as aminophylline and theobromine and found a shortening of the prothrombin time. Whether these results have any definite significance is questionable, in view of the undoubted limitations of the present tests for prothrombin. An attempt to introduce a good deal more accuracy into the present tests for prothrombin has been made by Deutsch,[122] who devised a photoelectric method for studying thrombin. This method deserves further investigation. Levy and Conroy[123] recorded the blood prothrombin (by the Smith bedside test) in patients receiving anesthesia. Ether anesthesia shortened the prothrombin time and therefore may be of some importance in the causation of postoperative thrombosis.

Hemophilia. Tocantins[124] reviews the various factors having to do not only with coagulation but also (which is quite as important) with preventing blood from clotting within the circulation. The coagulants are well known and include thromboplastin (cephalin), prothrombin and fibrinogen. The anticoagulant factors are less well known and may be listed as follows: an intact vascular endothelium, antithromboplastin, antithrombin and fibrinolysin. Blood clotting may be enhanced either by an increase in coagulation factors or by a decrease in anticoagulant factors. Tocantins believes that hemophilia is due to an excess of anticephalin (antithromboplastin) activity and not to a diminution in a thromboplastin-plasma material as maintained by the various workers at the Thorndike Memorial Laboratory of the Boston City Hospital. Lewis et al.[125] review their studies of the past decade in the physiopathology of hemophilia and conclude that the disease is due to a great deficiency in a globulin fraction of the plasma, which may be called the "antihemophilic globulin." In this paper, allusion is also made to Tagnon's work on the presence in normal plasma of a proteolytic fibrinolytic enzyme, having an as yet unidentified role in blood coagulation. Tagnon and his co-workers[126] contribute another article dealing with the fibrinolytic enzyme chiefly in hemorrhagic shock. Munro,[127] in common with Tocantins in this country and Pavlovsky in Buenos Aires, found an anticoagulant substance in the blood of a hemophiliac patient. The anticoagulant was found not to be antiprothrombin, heparin or antithromboplastin but was a lipoprotein apparently identical with the anticoagulant described some years ago by other observers. Fantl and Nance[128] found a circulating anticoagulant in the blood of a woman with severe hemorrhagic disease and a greatly prolonged coagulation time. It was determined that the material was an antithromboplastin.

The treatment of hemophilia has measurably advanced but not yet to the goal of complete control. Thrombin or fibrin foam will control to a large extent minor local bleeding, such as that from the gums, dental sockets, nose and skin, and even major operations have been performed with the use of these materials.

Employment of the antihemophilic globulin derived from the plasma fractionation program of Harvard Medical School has demonstrated a striking effect on the bleeding of hemophilia when only 100 to 200 mg. of the material is given intravenously. The daily use of this substance, however, is impractical. Van Creveld and Mastenbroek[129] present a preliminary report on a hemophiliac patient in whom the administration of 24 cc. of a 2 per cent solution of this fraction promptly reduced the coagulation time to normal and maintained it so for forty-eight hours.

The extraordinarily rare afibrinogenemia, which is usually congenital, is considered by Pinniger and Prunty.[130] In a case of severe hemorrhagic disease in a girl, these observers found a greatly prolonged clotting time and an almost complete lack of fibrinogen. Transfusion of reconstituted dried plasma was effective in controlling the bleeding and improving the fibrinogen deficiency. Rocha e Silva and his associates[131] demonstrated a great reduction in circulating fibrinogen in experimental shock produced by trypsin, peptone and ascaris extracts.

Hemorrhagic Capillary Disorders

Undoubtedly, the most frequent of the hemorrhagic disorders are those due to abnormalities of the capillaries. These occur in infectious diseases, deficiency states, at times with endocrine disorders and congenitally or idiopathically. The "devil's pinches" in soft-skinned women are often the cause for alarm but in reality have little if any significance. Whether they have anything to do with an

excess of circulating estrogen is questionable. All the various hemorrhagic factors in these cases, including platelets, prothrombin, clotting and bleeding factors, are normal. In rheumatic fever and acute glomerulonephritis purpuric manifestations are not rare. The platelets are normal, but apparently there is a more or less generalized disorder of minute blood vessels with seepage into the skin. Jones and Moore[132] discuss 3 such cases. Montgomery[133] found a definite increase in capillary fragility. No effect on the hemorrhagic disturbance or the capillary fragility was obtained with the use of vitamin P (derived from paprika).

A hemorrhagic disorder of mucous membranes with the formation of bullae and vesicles is reported by Foley[134] in a group of American and British prisoners of war confined to a Japanese prison camp. Crops of vesicles and hemorrhagic bullae developed on the buccal, palatal and tonsillar mucosa. No skin manifestations were present, and all the tests for hemorrhagic disturbance were negative. There was a quick response to the use of a high-protein, high-fat diet, but vitamins of various sorts were of no value. In occasional cases of hemorrhagic capillary disease one can make the diagnosis of Henoch–Schönlein purpura. In the Henoch type hemorrhagic manifestations are associated with intestinal disturbances, which may include abdominal pain, hematemesis and melena. Such a case is reported by Whitmore and Peterson.[135] In the Schönlein type joint manifestations are present. Since purpura, joint manifestations and intestinal disturbance may all coexist the designation of Henoch–Schönlein purpura is justified.

A heredity capillary defect is that known as hereditary hemorrhagic telangiectasia. Kushlan[136] reviews the historical and clinical aspects of the disorder and reports a case. The newly introduced material called rutin was used in a dosage of 40 mg. daily by mouth. There was "prompt" cessation of epistaxis, of gum bleeding and, finally, of gastrointestinal bleeding. The patient had been maintained for several months on a daily dosage of 20 mg. of rutin.

During the past year a number of articles dealing with rutin have appeared. This is a crystalline glucoside of quercetin derived from buckwheat leaves and flowers, tobacco leaf, rue herb and many other plants. Chemically, it is a derivative of flavone and related closely to hesperidin (vitamin P), citrin and ascorbic acid. It appears to have no toxic manifestations. Shanno[137] used the material in a variety of cases showing increased capillary fragility, and in all cases except those with thrombocytopenic purpura and allergic purpura there was a return to normal of the capillary fragility following the use of the drug. In a report to the Council on Pharmacy and Chemistry of the American Medical Association, Smith[138] takes this and other articles on rutin to task. The procedures for measuring capillary fragility are crude, and there is no complete agreement among the workers in the field on the reliability of the methods. It is probable that before another year has passed, the results with rutin therapy will have been fully assessed.

A queer hemorrhagic disorder characterized by a prolonged bleeding time is that of pseudohemophilia. The tendency to unusually profuse and continued bleeding after minor trauma resembles the bleeding of hemophilia. In about half the cases a definite family history of profuse bleeding in both females and males is obtained, with transmission by either sex. In such a case reported by Perkins[139] there was uncontrollable bleeding after minor operative procedures, and the development of large ecchymoses with slight trauma. The history of bleeding could be traced through five generations, and there was transmission from father to son. In addition to the abnormal bleeding time, a failure of capillary retraction (as previously noted by MacFarlane) was observed by means of capillary microscopy. Estren, Sanchez Médal and Dameshek[140] review the subject of pseudohemophilia and their experiences with 11 cases. The literature, clinical and laboratory features, diagnosis and therapy, together with a critical review of methods for the study of hemorrhagic disorders, are presented. The disorder, which is by no means rare, appears to be due to a congenital or hereditary defect of capillary retractility. In some ways it is more difficult to treat than hemophilia itself, since transfusions of blood are ineffective.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 33391

PRESENTATION OF CASE

A twenty-three-year-old man entered the hospital in shock.

About five years before admission the patient had several spells of unconsciousness, which at that time were thought to be petit-mal attacks. Systolic murmurs were noted at the base of the heart on several examinations thereafter. Four months prior to entry he began to experience throbbing frontal headaches, upper respiratory infection, with coryza, mild soreness of the throat and a cough productive of small amounts of sputum. At about the same time he began to have soreness of the left shoulder radiating down the arm for a short distance. Three weeks later there were several episodes of epistaxis, and he was given a sulfonamide for a week, during which time he had night sweats but no fever or chills. The soreness of the shoulder and other symptoms persisted, and he was admitted to another hospital one month after the onset of symptoms, or three months before admission to this hospital.

Examination at the other hospital revealed a pericardial friction rub but no valvular murmurs. An electrocardiogram showed flattening of the T segments in Lead 1, with inversion of the T waves in Leads 2 and 3. X-ray films of the chest revealed generalized enlargement of the heart, with thin arcuate calcifications overlying the left border. On admission the sedimentation rate was 65 mm. per hour; two and a half weeks later it was 35 mm. A blood culture was negative. The nonprotein nitrogen was 53 mg. per 100 cc. The Mosenthal test was normal. In the hospital the temperature fluctuated between 98 and 102°F. for thirty-five of the forty days he remained there. On the third day another x-ray film of the chest showed a marked increase in the size of the heart shadow, with increase of the pulmonary vascular markings. Symptomatically he improved considerably while taking salicylates, and they were continued throughout his stay, except for a period of one week. On the last three days in the hospital the pericardial fluid had subsided to such an extent that an apical systolic blow and a low rumbling diastolic blow were heard, the latter in the lateral decubitus position. He was discharged home, where he remained on salicylates for several weeks and continued to improve, regaining both strength and ambition.

Three weeks before entering the Massachusetts General Hospital, the patient had a mild upper respiratory infection with cough, nausea and vomiting. He also complained of soreness over the right upper quadrant of the abdomen. Two weeks later he re-entered the outside hospital, complaining of moderate dyspnea and slight edema of the feet, ankles and legs, which disappeared after a few hours' rest in bed. There was mild but definite cyanosis. Physical examination revealed pleural fluid bilaterally. The heart beat was regular at 130; no friction rub and no murmurs were audible. An x-ray film of the chest showed fluid in both pleural cavities, more on the right side than on the left, with collapse of the right middle and lower lobes. The heart shadow was considerably smaller than at the original examination.

Examination of the blood revealed a red-cell count of 5,000,000, with a hemoglobin level of 100 per cent, and a white-cell count of 8700, with 68 per cent neutrophils. The nonprotein nitrogen was 44 mg. per 100 cc. The urine gave a + test for albumin, and the sediment contained 3 to 5 red cells per high-power field. Six sputum specimens and the chest fluids were negative for acid-fast bacilli. Beta-hemolytic streptococci, alpha-hemolytic streptococci and *Staphylococcus aureus* grew from the sputum cultures. The chest fluid was sterile.

Two days after admission it was obvious that there was an increasing venous pressure, with engorgement of the neck vessels even in the sitting position. There was a paradoxical pulse. The systolic blood pressure was 105; the diastolic point was difficult to determine, but was thought to be 95. The pleural fluid had increased bilaterally. The liver was palpable three fingerbreadths below the costal margin but was nontender. There was a productive cough, and later the sputum became bloody. Paracenteses were performed twice on the right, with marked improvement in the respirations, although the venous engorgement persisted. A third paracentesis produced 800 cc. of fluid, this time without the improvement that had been noted previously. On the seventh hospital day an attempt was made to obtain pericardial fluid. On inserting the needle into the fifth left interspace near the sternum, a definite grating sensation was felt just as the needle came in contact with the heart. Five cc. of blood-tinged fluid was obtained. Another attempted paracentesis a little farther laterally in the same interspace failed to obtain fluid.

On the day of the pericardial paracentesis the patient was transferred to this hospital.

On arrival, he was breathing with great distress and was cyanotic, anxious and confused. Cyanosis was most marked in the hands and feet. The blood pressure and pulse were unobtainable. The skin was clammy. The neck veins were slightly distended,

without visible pulsations. Veins over the extremities were collapsed. The cardiac apical beat was not palpable, but to percussion the heart seemed enlarged about 10 cm. to the left of the midsternal line. The sounds were distant but regular at a rate of 80. There were dullness and decrease of breath sounds over both bases. No rales were heard. The liver extended 3 to 4 cm. below the costal margin and was tender. The sacral and scrotal regions were edematous. No reflexes could be obtained.

An x-ray film of the chest showed fluid in the left pleural cavity. The heart shadow had not changed since the last examination.

Two attempts were made to tap the pericardium through the xiphoid approach shortly after admission. No pericardial fluid was obtained. Death occurred a few hours after entry.

Differential Diagnosis

Dr. George W. Pickering*: This is quite clearly a case of acute pericarditis in a man of twenty-three. I suppose the possible causes of acute pericarditis in such an individual are first, rheumatic fever, second, tuberculosis and, third, some rather less common ones, such as a septic condition, an infarct of the heart and uremia. Cardiac infarct can be excluded. Uremia can also be ruled out without further discussion because of the blood chemistry and the subsequent course. I think that we can also exclude sepsis. We are not given any details about the pericardial fluid, but we know that the pleural fluid was sterile, that the blood culture was sterile and that there was no leukocytosis. That leaves, as the chief possibilities, rheumatic and tuberculous pericarditis.

Let us begin with the first episode, which is in the past history. He had a number of petit-mal attacks or, rather, attacks of unconsciousness that were thought to be petit-mal attacks. Unfortunately, we know very little about these attacks. We know nothing about the duration, the frequency and so forth, whether they were preceded by an aura, or whether they were preceded by any definite events in his environment. In other words, were they dizzy attacks or were they true petit-mal attacks? If they were epileptic attacks, we have no family history or symptoms of a cerebral lesion. I had thought this might possibly fit into tuberculosis — that these attacks might result from a tuberculoma of the brain. But I do not believe that we can say any more than that.

The next episode that he had was at the age of eighteen. He is now twenty-three and comes in with fever and upper respiratory infection and soreness of the left shoulder, which to my mind sounds like pain due to involvement of the phrenic nerve, but there is no evidence in the history of increase of pain with respiration, such as one gets in many cases when the diaphragm itself is involved, particularly on the pleural side. Then the signs on admission show quite clearly that he had an acute pericarditis. There was a friction rub, followed by enlargement of the heart shadow. This is actually the first x-ray film. There is a peculiar feature here, a thin arcuate calcification overlying the left border of the heart shadow. These are just visible but they are possibly about 3 or 4 mm. in from the edge of the heart shadow. It is tempting to speculate on these. They are not due to old cardiac infarction. They do suggest possibly that there had been a preexisting pericarditis, and I should have guessed that tuberculosis was the cause of that. This film shows enlargement of the heart shadow, probably due to pericardial fluid, although I am not expert on radiologic diagnosis. This was obviously regarded at the time as rheumatic and was treated by salicylates. It is stated that he improved considerably while taking salicylates, but it is also stated that the temperature ranged between 98 and 102°F. for thirty-five out of his forty days in the hospital, and my interpretation is that he did not respond to salicylates. That, I think, is the first point against rheumatic fever as a diagnosis. The second is that this was an adult; in most adults one would expect some symptoms and signs in the joints, but those were absent. There is one other point that I should like to comment on: if this were an effusion into the pericardium, I should have expected at that time that a marked increase in venous pressure would have been noted in the neck. There is no mention of that in the record. Then we come to the noises that were heard in the heart. After the fluid had started to subside, an apical systolic blow and a low, rumbling diastolic blow were heard, the latter in the lateral decubitus position. Did this mean valvular disease? I think Dr. Paul D. White and Dr. T. Duckett Jones† have shown here that one can get diastolic murmurs associated with cardiac enlargement. Does that then mean cardiac enlargement in this case, quite distinct from the pericardial fluid? If it does, then it argues for involvement of the heart muscle, which is strongly in favor of rheumatic heart disease. On the other hand, I think that it is rather difficult sometimes to distinguish a pericardial rub from a murmur, and I am not at all sure this may not have been a to-and-fro rub as opposed to the apical diastolic and rumbling diastolic blow reported.

The patient then went home and shortly afterward returned to this same hospital, where he was found to have signs of venous congestion. At any rate, he had edema; although it is stated that the venous pressure did not rise until two days after admission, I suspect that it was present on admission. He had fluid in both pleural cavities, with collapse of the right middle and lower lobes. He did not have anemia, the hemoglobin being 100 per cent; that is against rheumatic disease. There

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was no leukocytosis. We have not heard anything about that before; it is slightly against rheumatic disease. The case was clearly being regarded as one of possible tuberculosis, because the sputum was examined repeatedly. The specimens were negative for acid-fast bacilli, and that is the rule in tuberculous pericarditis. Fluid was obtained from the pericardium, but unfortunately we are told nothing about it. I think we can assume that it was not a septic fluid. The patient got worse following the dry taps, was admitted to this hospital and perished within a few hours.

My diagnosis is tuberculous pericarditis. I think that it was acute, but possibly there had been some older element, because of the calcifications in the x-ray films. He probably had tuberculosis of the lung to account for the bloody sputum toward the end of his existence. He may have had tuberculoma of the brain, although there is only the very slightest indication for it. He probably died of terminal miliary spread, because that is the usual course in most cases. You will note that there is no definite evidence for that diagnosis. It is simply suggested because most cases of pericarditis that I have seen occurring in young adults and children with no other evidence of rheumatic disease, with no other evidence of involvement of anything else but the pericardium, with no etiologic factor discernible from examination of the fluid and with a duration of four months or more, have usually turned out to be tuberculous.

Dr. Tracy B. Mallory: Would you like to give your impression, Dr. Williams?

Dr. Conger Williams: At the time of admission our problem was treatment of the emergency. The patient was actually in a state of shock. No pulse was perceptible. He was deeply cyanotic, especially in the legs and hands. Of course our first consideration was cardiac tamponade to explain this picture, but one thing that bothered me about that diagnosis was the absence of marked distention of the neck veins. Dr. DuToit suggested that perhaps the absence of distended neck veins could be explained by diminished cardiac output. We also considered the possibility of an advanced rheumatic myocarditis with peripheral vascular collapse, because of the previous story of murmurs. Nevertheless, we thought there was an excellent chance that this man had pericardial tamponade and should, therefore, be tapped. This operation was performed by Dr. Soutter. He was unable to get any fluid from the pericardium. The patient died soon afterward.

Dr. Paul D. White: May I ask if there is certainty that the calcification is in the pericardium or in the heart and not elsewhere?

Dr. Toufic H. Kalil: Not without fluoroscopy. These films were done on the outside, and a lateral film was not taken. That may well be behind the heart.

Dr. White: I should like to point out that it is possible to have both pericarditis of a chronic constrictive nature, possibly tuberculous in origin, and rheumatic heart disease in the same case. We have seen such cases but they are few and far between and apparently coincidental.

Dr. Pickering has looked up and seen quite a few cases of tuberculous pericarditis, and I should like to ask him whether the heart is enlarged in those cases and whether the subjacent or subpericardial myocarditis is diffuse enough to give the picture of an enlarged heart and to produce murmurs with no specific changes in the electrocardiogram. Of course the changes often found in the electrocardiograms in such cases are in part due to the subpericardial myocarditis, but perhaps there is more than that. In our chronic constrictive pericarditis cases there was cardiac enlargement in something over half. It seems as if the myocardium, as well as the pericardium, was involved.

Dr. Pickering: I am not sure that I can answer that. I am certain that the myocardium is abnormal. At any rate, by the time the fluid is absorbed in tuberculous pericarditis it certainly behaves like that, in the sense that it does not respond in the ordinary way to changes in venous pressure, and my "pathologist friends" tell me that the myocardium looks abnormal. Nor am I able to answer the question regarding the heart size. We really see so few of these that we only get definite evidence about the size of the heart if we replace the fluid with air or if the patient is examined post mortem.

Dr. Edward F. Bland: Would Dr. Pickering accept the migrating pleuritis, in addition to the pericarditis, as favoring an acid-fast background?

Dr. Pickering: If you can accept this as an inflammatory pleural effusion, certainly. The difficulty is, I suspect, that you have throughout this case a congestion arising from pericardial tamponade or changes in the pericardial cavity, and it is difficult, I think, without seeing the patient and personally examining him from all these angles, to come to this conclusion. I think the explanation is correct but would not like to bank on it at the present time.

Clinical Diagnosis

Rheumatic myocarditis.
Cardiac tamponade?

Dr. Pickering's Diagnosis

Tuberculous pericarditis, probably acute on a more chronic background and probably accompanied by pulmonary tuberculosis and possibly a terminal miliary spread.

Anatomical Diagnoses

Acute and chronic tuberculous pericarditis.
Tuberculosis of lung and bronchial and mesenteric lymph nodes.

Pathological Discussion

Dr. Mallory: Post-mortem examination showed a pericardium 5 to 10 mm. in thickness, the thickening being due almost entirely to fibrosis, although there were a few spots with slight calcification of the pericardial sac. Approximately half the pericardial cavity was obliterated. There was a pericardial space left in two pockets amounting to a third or a half of the original sac. In that, we found just a few cubic centimeters of blood-stained fluid that did not seem to be enough fluid to consider that he had cardiac tamponade. The heart itself was very small; the heart and pericardium together weighed 450 gm. We have not separated the heart from the pericardium, but I doubt very much if the heart weighed over 275 gm.; it might even be 250 gm. The valves were entirely normal. We found a number of large caseous bronchial lymph nodes, one caseous node in the mesenteric area and one small focus of active tuberculosis in the lung but no general miliary process. Sections from the pericardium and epicardium showed extremely marked fibrous thickening and inflammatory changes, and just beneath the epicardium in one spot a rather characteristic single miliary tubercle. I think we have enough to confirm the diagnosis of tuberculous pericarditis beyond a doubt.

Addendum by Dr. Pickering. I find this case of peculiar interest. A week previously I had communicated in the Ether Dome the results of work by Dr. T. Holmes Sellors, Dr. G. W. S. Andrews and myself, which had led us to conclude that, in Great Britain at least, most cases of constrictive pericarditis are of tuberculous origin. Briefly we observed the following: that out of 16 cases of tuberculous pericarditis observed over periods up to six years, 14 developed signs of constrictive pericarditis, 1 presented a persistent effusion and in only 1 was there no residual sign of pericardial disease; that acute tuberculous pericarditis unassociated with tuberculous pleurisy or ascites may give rise to relatively little subjective disturbance; and that the only 2 of our 7 patients with septic pericarditis who recovered from the acute stage presented no signs of constrictive pericarditis clinically or radiologically during the next four years. Calcification of the pericardium is common in constrictive pericarditis; this is the first case known to me personally in which post-mortem examination has revealed clearly both pericardial calcification and tuberculous pericarditis. It therefore adds weight to my belief that tuberculosis is a common, and I think by far the most frequent, cause of constrictive pericarditis.

CASE 33392

Presentation of Case

First admission. A fifty-one-year-old woman entered the hospital complaining of epigastric pain, nausea and vomiting of five months' duration. The pain was not related to meals and not relieved by food. Tarry stools had occasionally been noted. Fifteen years before admission a posterior gastroenterostomy for ulcer and a cholecystectomy had been performed. From this time until six months before entry the patient had been relatively free of ulcer symptoms.

Physical examination was essentially negative.

Examination of the blood revealed a red-cell count of 4,200,000, with a hemoglobin of 60 per cent, and a white-cell count of 8000. The urine was clear, but the sediment contained numerous red cells. Subsequently, four other examinations of the urine were negative. The stools were guaiac negative on three occasions. The gastric acidity was normal.

A gastrointestinal series showed no active ulcer. The left kidney appeared enlarged. Intravenous and retrograde pyelograms showed a mass in the upper left kidney. An x-ray film of the chest was normal. The patient was transferred to the Urological Service, where the left kidney was removed through a lumbar incision. The upper pole of the kidney was occupied by a 8.0-cm. by 5.5-cm. renal-cell tumor (hypernephroma), which had not broken through the kidney capsule.

Second admission (thirteen years later). The patient was asymptomatic until three months before admission, when grossly bloody bowel movements had appeared. At other times the stools were black. For two months she had been weak and tired, with some pain in the left lower quadrant. She sometimes felt a lump in the left lower quadrant. The epigastric pain also recurred and was relieved by food. Three weeks before entry a barium enema at another hospital had shown a "bowel tumor."

Physical examination revealed tenderness in the left lower quadrant, which prevented deep palpation. No mass was felt.

The urine was normal, as were the nonprotein nitrogen, serum protein and prothrombin time. The hemoglobin level was 12.4 gm.

Examination of the x-ray films brought in by the patient showed a shadow the size of a kidney in the left upper portion of the abdomen. A barium enema disclosed a persistent filling defect in the descending colon that had the appearance of a polypoid neoplasm (Fig. 1). There was no obstruction to the passage of barium. The bones were normal.

On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Laurence L. Robbins: In summary, this sixty-four-year-old woman had been complaining of bloody bowel movements for three months. There were associated symptoms of weakness, dizziness and left-lower-quadrant pain, with an abdominal mass at one time or another. At thirty-six years of age a gastroenterostomy and cholecystectomy

had been performed, and at fifty-one a hypernephroma of the left kidney had been removed.

The first point that we can be sure of, in looking at this x-ray film, is that a barium enema had been given, and I should say that the patient was not particularly well prepared. There is a shadow extending well beyond the bowel; it apparently lies in close contact with the descending colon. Extending into the lumen of the descending colon is a small lobular mass, which is perhaps better seen on this film. I do not know whether this is a postevacuation study or not, but gas, which is not seen in this first film, is present and the film probably represents a double-contrast enema after the injection of air. Here again we see the mass. Most of my discussion will hinge on whether this shadow beyond the confines of the bowel and this one protruding into the lumen of the bowel are parts of the same lesion. There is, in addition, another shadow — a rather well defined mass — in the region where the left kidney is usually located.

I should like to take this opportunity to point out the fact that frequently after nephrectomy a shadow is visible on the plain film of the abdomen that is perfectly consistent with a normal kidney shadow. That is probably what happened in the case under discussion. At least, I assume that the shadow is due to organized blood clot or fibrous tissue that remained after operation. But the fact that there is a shadow in that area does not mean that the kidney was not removed and that another abnormality was present.

FIGURE 1. *Roentgenogram following a Barium Enema.*
The upper arrows point to the shadow described as lying in the kidney bed. The lower arrows indicate the mass involving the descending colon.

DR. BENJAMIN CASTLEMAN: How long does this shadow remain?

DR. ROBBINS: For years. I cannot be certain because there is no plain film, but I think that this

particular shadow corresponds to the persistent postoperative one frequently seen.

To go back to the lower shadow protruding into the descending colon, could this have been tied up with some inflammatory process such as a stromal ulcer with abscess formation and perforation into the colon? It seems unlikely from the data in the history. Likewise, I do not believe that other inflammatory processes, such as hyperplastic tuberculosis and amebic granuloma, need be considered. An infected diverticulum could give this appearance, but there is slightly more lobulation and more protrusion into the lumen than one would expect in diverticulitis. Also, there is no other evidence of diverticulum that can be seen on these films. One should consider a foreign body as a possibility, but that again seems unlikely. Endometriosis can produce a shadow similar to this, but it is somewhat higher than is usually found and, at the age of this patient, endometriosis is improbable. Furthermore, endometriosis would not account for the melena.

So far as tumor is concerned, the first thing to consider is whether this was an adenomatous polyp, which immediately means cancer until proved otherwise. Or was this extrinsic shadow a secondary tumor that extended from a primary cancer in the bowel? That is not impossible, although it is extremely unusual, from the x-ray standpoint, to see a sharply circumscribed mass of nodes adjacent to the tumor. This is much too smooth for the ordinary mass of lymph nodes, so that I am inclined to rule out the possibility of a primary carcinoma.

Could this have been metastasis or extension from the hypernephroma? The mass was somewhat lower than the area in which the descending colon was in contact with the kidney bed; metastasis would not be impossible, however, and it is difficult to be certain of the observation from the number of films at hand. I shall take the chance that the mass involving the bowel was entirely intraperitoneal, because if this mass arose from the kidney area and extended to the bowel, I think that the shadow of the psoas muscle would have been lost in that area where the mass overlies it, and the shadow of the psoas muscle is present. I cannot exclude metastasis from hypernephroma, but I have not seen cases in which the bowel was involved.

Certainly, we must consider the possibility of lymphoma. Here, again, unless it arose from the nodes in the mesentery or the mesocolon and extended into the bowel, this appearance is atypical. It could have arisen from the small bowel, but there is nothing in the history or the x-ray films to indicate small-bowel disease. Finally, it is somewhat more of a polypoid lesion than the usual lymphomatous involvement of the bowel.

Tumors of connective-tissue or smooth-muscle origin certainly cannot be completely excluded. The mass is relatively smooth and appears to be intramural and to involve the mucosa. These tumors are prone to bleed rather profusely, as this one did.

There is another tumor that should be considered purely from what is seen on these films — that is, a carcinoid. Often the bulk of the tumor lies outside the bowel wall, producing in many cases a fairly sharply circumscribed mass that may be smooth. By and large, however, the lesions do not involve the mucosa, and there is no bleeding in the cases with which I am familiar. Also, the history in this case was too short, because a carcinoid usually is a slowly growing tumor. I have never seen one in this location in the bowel.

Actually, this is as far as I have a right to go. All I can say is that there was a tumor that involved the mucosa and a large mass extrinsic to the bowel. If this problem could be studied from spot films, even though fluoroscopy was excluded, there would be more opportunity of determining what this mass was.

From now on whatever I say is pure guesswork. I believe that there are three things to be considered primarily: extension from a hypernephroma, tumor of connective-tissue or smooth-muscle origin and carcinoid. I do not believe that we need to consider a primary carcinoma or lymphoma seriously. I believe that the most probable diagnosis is a tumor of connective-tissue or smooth-muscle origin.

Dr. Fletcher H. Colby: I wonder why a chest film had not been taken. The lung is the favorite site for hypernephromas to metastasize.

Dr. Castleman: Chest films taken in the Follow-Up Clinic in the Out Patient Department three years previously were negative. The patient had not been seen since that time.

Dr. William Clark: Has recurrence of hypernephroma been recorded in that long an interval?

Dr. Robbins: Yes.

Clinical Diagnosis

Tumor of descending colon.

Dr. Robbins's Diagnosis

Spindle-cell tumor of descending colon.

Anatomical Diagnoses

Leiomyoma of descending colon.

Recurrent renal-cell carcinoma, with invasion of adrenal gland.

Pathological Discussion

Dr. Castleman: Fairly extensive adhesions were found throughout the left side of the abdomen. The left colon, which contained a mass the size of a baseball, was freed laterally, and another mass was felt slightly higher in the left gutter. At first it was believed that this second mass was located in the pancreas, but on further dissection it proved to be in the adrenal gland. The entire mass was removed.

Grossly, it measured 9 by 5 by 3 cm. (Fig. 2 and 3), and microscopically it proved to be renal-cell carcinoma involving the adrenal gland.

The colon was then resected. The intraluminal portion of the intestinal tumor was relatively small,

FIGURE 2. *Photograph Showing the Two Tumors.*
That on the left is a section of the descending colon, with the intraluminal portion of the tumor. That on the right is the left adrenal gland, with enlargement due to recurrent renal-cell carcinoma.

measuring only 2 cm. in diameter; it was covered with mucosa but was somewhat hemorrhagic (Fig. 2). The extraluminal portion was much larger, about 6 cm. in diameter, and when sectioned the tissue bulged exactly as a fibroid of the uterus bulges when it is cut (Fig. 3). This bulging is due to the fact that the tumor is held under marked tension within its capsule and that when the capsule is cut, the tumor emerges. Microscopically, this tumor proved to be a leiomyoma. Dr. Robbins was therefore correct in his analysis of the shadow involving the bowel. The upper shadow, which he considered to represent merely the site of the previous nephrectomy, was the recurrence of the hypernephroma.

A PHYSICIAN: Do you think that there was a metastasis to the adrenal gland?

DR. CASTLEMAN: I favor a recurrence with extension into the adrenal gland rather than a metastasis. There was still some normal-appearing adrenal tissue on one surface of the tumor.

DR. WILLIAM BECKMAN: How do you explain the bleeding?

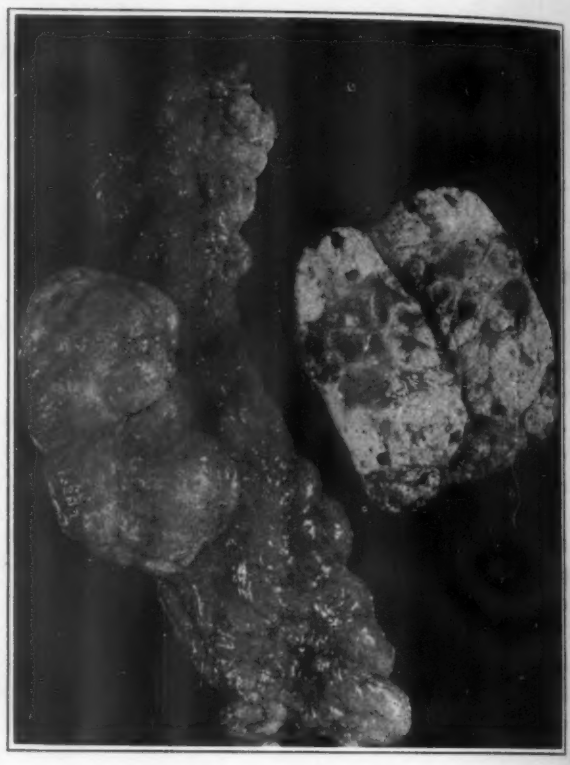

FIGURE 3. *Photograph Showing the Cut Surfaces of the Two Tumors.*
That on the left is the cut surface of the extraluminal portion of the tumor in the colon; note the bulging following sectioning. That on the right is the cut surface of the tumor mass involving the left adrenal gland.

DR. CASTLEMAN: From the leiomyoma.

DR. BECKMAN: But the mucosa was intact.

DR. CASTLEMAN: That is not rare with bleeding intramural tumors of the stomach. At the time of operation there may not have been any ulceration. A small erosion may have healed during the preoperative period.

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ROBERT NASON NYE

Again, within a short space of time, the *New England Journal of Medicine* announces with sorrow the passing of a leader. Dr. Robert Nason Nye, its managing editor since 1937, succumbed on September 10 to an illness that, insidious in its onset and inevitable in its conclusion, was mercifully brief.

Dr. Nye assumed the editorship of the *Journal* in 1937 on the retirement of Dr. Walter Prentice Bowers, whose death a few weeks ago was recorded on this page. Where Dr. Bowers left off Dr. Nye began his own task, and gave to the *Journal* a skilled and devoted guidance that has brought it to a leading position among the medical periodicals of the world.

There are certain characteristics that distinguished Dr. Nye from lesser individuals — his robust personality, his clear understanding, his intellectual integrity. He never compromised with his conscience. In the shock of his loss we realize that we shall not soon find one to take his place.

TOXICITY OF STREPTOMYCIN

From the reports of its clinical use to date[1, 2] it is apparent that streptomycin will remain the treatment of choice in many infections due to gram-negative bacilli and to *Mycobacterium tuberculosis* until a better agent is found to replace it. The major drawbacks to its more widespread use, aside from its high cost, are the frequency with which development of bacterial resistance appears during its administration and the toxic effects that it produces, particularly when it is used in large doses or over long periods. Some reports dealing particularly with the otic complications of streptomycin have already appeared.[3, 4] Detailed observations of the toxic effects of this agent in a small group of patients who were treated for tuberculosis over long periods at the New York Hospital are particularly worthy of comment.[5]

The patients received 3 gm. daily in eight intramuscular doses of 375 mg. each of an almost pure streptomycin salt. The levels of streptomycin in the serum ranged between 7 and 30 microgm. per cubic centimeter at the end of the three-hour interval between injections. It was considered advisable to interrupt treatment because of toxic manifestations in only 2 patients; both had an anaphylactic type of reaction, and in each case it was possible to resume treatment later.

There was remarkably little irritation at the site of the intramuscular injections in spite of their large number and frequency. Repeated intrathecal injections of 0.1 gm. in 10 cc. of isotonic salt solution were also well tolerated. There was usually a moderate pleocytosis from these injections in patients who had no evidence of central-nervous-system disease, and occasionally there was headache, nausea and vomiting or some pain in the legs, the latter presumably due to transient irritation of nerve

roots. Amounts of 0.2 to 0.375 gm. intrathecally, however, produced untoward reactions, particularly after such doses had been given repeatedly for several weeks. In such cases there was somnolence, slowing of the respiratory rate and retention of urine. These symptoms usually lasted twelve to twenty-four hours and then disappeared. There were no sensory changes or persistent sphincteric disorders. Nystagmus was occasionally noted immediately after the intrathecal injection. Appreciable concentrations (4.5 to 17 units per cc.) of streptomycin were always present in the cerebrospinal fluid forty-eight hours after the intrathecal injection of these large doses.

Symptoms of vestibular dysfunction of variable severity appeared uniformly between the seventeenth and the twenty-fifth day of treatment. Complete symptomatic recovery eventually occurred in all subjects. This recovery was presumably a result of activation of compensatory mechanisms rather than of restoration of labyrinthine function.

Deafness developed in 2 of 16 patients treated for four months, and in 3 others subsequently treated with the same preparations of streptomycin. Bilateral nerve deafness, amounting to from 50 to 100 per cent, occurred in 7 of the first 100 patients treated with streptomycin at the New York Hospital.[6] No tinnitus or impairment of hearing during or subsequent to the streptomycin treatment was observed in any of the other subjects, and no other neurologic disturbances were discovered in these patients. Five of the 7 patients with deafness had undergone prolonged intrathecal administration of streptomycin, and the other 2 had marked renal insufficiency, suggesting that the concentration of streptomycin in the central nervous system may be an important factor in the occurrence of deafness. Preliminary studies suggest that the site of this toxic reaction is the brain and that it is associated with liquefaction necrosis of the ventral cochlear and inferior vestibular nuclei.[7] Since these patients may also have had central-nervous-system lesions, the part played by such lesions, at least in the deafness, cannot be ruled out.

The vestibular disturbance accompanying streptomycin therapy is a most unusual complication of drug therapy. Farrington et al.[5] describe this disturbance as follows:

> . . . This reaction is characterized by the appearance of a mild headache, which disappears within twenty-four hours and is followed by the development of symptoms which resemble vertigo. The sensations differ from vertigo in that they seem to occur in a linear rather than a circular plane. At the completion of a sudden movement, such as reaching for an object, sitting up or leaning to one side, the afflicted person feels as though the movement was continuing in the same direction in which it had been going. Thus he experiences the sensation either of past pointing or of falling in the direction of the previous movement. Occasionally, a momentary delay in focusing the eyes after a sudden change in position will be noted. At the height of the reaction one patient displayed striking pendulum movements, similar to those observed in labyrinthectomized animals. When he assumed the erect sitting position suddenly, he swayed back and forth rhythmically for approximately sixty seconds.
>
> There was a considerable variation in the intensity of the vestibular dysfunction experienced by the different subjects. . . . At the peak of the reaction these subjects [the ones with moderate or severe involvement] were unable to sit up in bed unassisted and with the slightest motion were acutely uncomfortable even when lying flat. They were frequently nauseated, and occasionally they vomited. The symptoms usually persisted in an acute form for seven to ten days and then subsided almost entirely. The disappearance of the acute symptoms occurred with striking rapidity, sometimes within a period of twenty-four hours. In no instance, however, did complete recovery occur with the subsidence of the acute symptoms. Instead, the subjects entered into a phase in which the symptom was absent during ordinary activity but could be evoked momentarily by an unusual stimulus, such as an abrupt shaking of the head. . . .
>
> In general the stage of latent vestibular dysfunction persisted for approximately sixty days and then disappeared. During the fourth month of therapy all subjects except one were completely free from these symptoms while reclining or sitting erect in bed. . . . Ataxia was absent as long as these persons could orient themselves visually with any fixed object. A staggering gait was present, however, when they attempted to walk in the dark or with closed eyes. In these particular instances the symptom has not been disabling and has slowly diminished in intensity during the nine months since the cessation of therapy. In no instance was streptomycin therapy interrupted because of vestibular dysfunction.
>
> . . . nystagmus was seldom encountered. Only one patient . . . manifested a sustained nystagmus, although in several other subjects fleeting nystagmoid movements of questionable significance were observed. In [another] patient . . . a rotary nystagmus was observed.

The renal complications, although not severe and probably of no great significance, are nevertheless of some interest. A few patients showed transient reduction in renal function associated with nitrogen retention. Casts of various types appeared intermittently in the urine in the majority of cases; they were present when a highly acid urine was excreted and usually disappeared when the urine was alkaline.

Sensitization reactions were encountered oftener during treatment with streptomycin than with sulfonamides or penicillin. They were manifested chiefly by fever, dermatitis and eosinophilia. The last was either intermittent or sustained, ranged from 5 to 39 per cent and was noted in the great majority of the cases.

McDermott[6] also studied patients treated with impure lots of streptomycin. From a comparison of the reactions in such cases with those observed in patients treated with pure streptomycin it was concluded that the histamine-like reactions, irritations at the sites of injection and possibly sustained febrile reactions were not caused by streptomycin but by impurities, which are removable by refinements in the process of manufacture. All the other manifestations of toxicity that have been observed after the use of impure streptomycin have also occurred during the administration of the highly purified preparation of the drug.

From these observations, McDermott concluded that the immediate toxicity of highly purified streptomycin on long-continued administration is sufficiently low to justify the use of the drug in the treatment of serious and protracted infections, such as most forms of tuberculosis. Since streptomycin, however, can produce serious toxic reactions he believes that it is not advisable to use the drug in the treatment of benign infections with a generally favorable prognosis, such as minimal pulmonary tuberculosis and chronic brucellosis.

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"MERCY CARS"

THE accounts that appear in the daily press from time to time describing the record-breaking speed made by so-called "mercy cars" on their way to one or another of the large metropolitan hospitals, accompanied by police escort and heralded by the wailing of sirens, are to be deplored. Physicians who, in their early years of training, were driven through city streets in a hospital ambulance appreciate the thrill of such a journey, not only to those in charge of the ambulance but also at times to the patient. And who does not pause, with a certain boyish thrill, to watch an ambulance go by? Ever so often, however, this excessive and, as a rule, unnecessary speed results in death or serious injury to the occupants or to innocent bystanders.

Racing over congested highways does shorten the trip to the hospital, but it is only occasionally that the minutes gained are of benefit to the patient; indeed, such a trip may be truly harmful to one who is seriously ill. Thus, a physician, when he learned that a patient with a compound fracture of the skull was being rushed to his hospital under police escort, sent out word through appropriate channels that the police escort was to slow the ambulance down to below thirty miles an hour, believing that this was better for the patient and all concerned. He then took pains to be sure that the necessary measures to ensure immediate treatment on arrival at the hospital were taken.

The matter has its entertaining side. Recently, a small patient who had swallowed a penny was being rushed to a metropolitan hospital. En route, the automobile was in collision with another, and five occupants of the cars were taken to a small local hospital because of minor injuries. On arrival at the hospital the penny was found on the floor of the mercy car. Whether the shaking up of the ride or that of the accident was the effective therapy was not discovered. But neither, as a matter of fact, is recommended as a specific form of treatment in similar cases.

Certainly, a speed of eighty or even sixty miles an hour over roads, summer or winter, is difficult to justify except in extreme cases, and the attending publicity, even though no accident results, seems in poor taste. Such publicity should be minimized, and better still, the public should be made aware of the fact that, generally speaking, extreme speed is unnecessary and may be harmful to the patient and to others.

A HUNDRED YEARS AGO

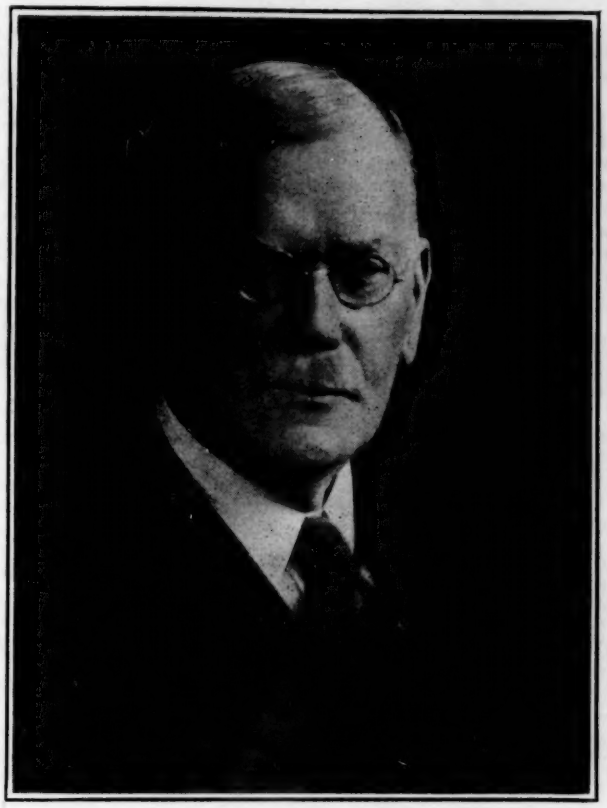
With the multiplication of hospitals, dispensaries and charities of all descriptions, and the onward and upward march of pure medical science, there have grown into notice, and favor, too, institutions for providing families with the necessaries of life, when the strong arm on which a wife and children placed their whole dependence for daily bread, is weakened, and the willing heart is overcome with assaults of disease. There is an office in Tremont street, where by the payment of from four dollars seventy-five cents to nine dollars fifty cents a year, a man, from twenty-five to fifty-two years of age, may draw weekly from four to six dollars, when an invalid. Besides the great benefit to the insured, there would be no complaint by the physician of poor practice by loss of bills, were the custom a general one, as it should be, of being fully insured. A scheme so admirable as this, and withal so strictly economical, addresses itself at once to the understanding; and we hope, therefore, that the benefits of that excellent institution, the Massachusetts Health Insurance Company, may be appreciated by the intelligent people of New England. — Mr. L. M. S., while engaged in his usual avocations, was attacked with severe pains in his bowels, and nausea, at noon. He was obliged to leave his business and return home. The pain was in the right hypogastric region, not constant, but intermitting, like colic pain. He took a cathartic, which was retained in the stomach three hours and a half, and was then vomited, without having any effect on the bowels. An enema was ordered, which moved the bowels freely, with much relief. In two or three hours after the enema, the spasmodic pain returned in the same spot on the right side, shooting through to the back. It became necessary to resort to opiates every few hours to relieve pain. He continued to vomit frequently, at first dark mucus and such drinks as he had taken, and finally vomitus colored by particles of dark blood. His pulse became more rapid and less distinct, his skin moist and cool. He continued to fail until he breathed his last. An autopsy was made by Dr. J. B. S. Jackson. The caecum and ileum were highly inflamed, but the cause of the inflammation was not discovered till the caecum was dissected from its bed in the iliac fossa; the appendix then was found closely adherent to the caecum, in an ulcerated and gangrenous condition. Within the appendix were two small masses of fecal matter in a hardened condition; these had ulcerated completely through the coat of the appendix. How long the appendix had been in this unnatural condition, it is impossible to say. It was probably of long standing, but not congenital. He had for the last three or four years complained of pain and lameness in that region when more than usually fatigued; as to the length of time the fecal matter had been retained, no definite opinion can be given. — Readers will doubtless recollect that a variety of comments appeared in this Journal on the dinner served up for the Massachusetts Medical Society. At the last anniversary it is believed the dinner proved quite satisfactory. It seems, however, that something more is wanted to give a gusto to the festivities of the occasion. A gentleman declares that a band of music is the one thing needful to give life to a very dull meeting. The mere act of eating oyster pie and fried cabbage is not sufficiently animating to stir up the enthusiasm of four hundred physicians. So next year he votes for music. — Dysenteric affections are very general as they always are at the season of the coming in of new fruits; yet the number of deaths has been comparatively small, which gives reason to suppose that physicians, when seasonably consulted, have been successful in their prescriptions. — Otis Clapp, of Boston, has in press a "New Manual of Veterinary Medicine on the Homeopathic Treatment of the Horse, the Ox, the Sheep and the Dog and other Domestic Animals," by F. A. Gunther. Translated from the third German edition, with considerable additions. Surely this is an exhibition of folly, remarkable even in imaginary science. — John Ur Haezer, of Sullivan Co., Tenn., aged 114, walked, recently, half a mile to vote! He has voted at every presidential election that has been held in the United States. — The American Geological Society was in session in Boston last week at the Marlboro' Chapel. There was a strong representation of the science of the country present. It was noticeable that quite a number, if not a majority of the Society hailed from the medical profession. The true way of keeping up an interest in any branch of natural science is to bring those together frequently who are devoted to such pursuits. It is only by comparing labors and freely interchanging thoughts, that progress can be made in elevated branches of knowledge. — An eminent physician of New Orleans was called recently, it is said, to Madame A., ill of a slight fever. He wrote a prescription, the directions of which were followed strictly, and a short time only after the medicine for Madame A. was taken, she expired. It subsequently appeared that he had ordered *morphine* instead of *quinine*. The error, which is only explained by the distraction arising from the pressure of professional engagements, is irreparable. — Extracted from the *Boston Medical and Surgical Journal*. August-September, 1847.

R. P.

WALTER PRENTICE BOWERS

1855–1947

Walter Prentice Bowers was born in Clinton, Massachusetts, on May 19, 1855, one of the eight children of the Reverend Charles Manning and Ella (Damon) Bowers. At the time of his birth his father's yearly salary as minister of the First Baptist Church was five hundred dollars. At no time did it permit any unusual expenditures on the education of so large a family, and the three years after Walter's graduation from high school found him working in a drugstore, earning the money to put himself through Harvard Medical School.



He matriculated in the school in 1876 and graduated with honors in 1879. After serving for a time in the Out Patient Department of the Massachusetts General Hospital, he joined the staff of the Worcester Lunatic Hospital, now the Worcester State Hospital and settled in Lancaster to practice. Ill health forced him to resign from this post in 1881, and he moved to Clinton, where he established the practice that was to occupy him continuously until his death. In 1880 he married Helen M. Burdett, of Clinton, whom he survived. They had no children.

Dr. Bowers was in every way a leading citizen of his community. He founded the Clinton Hospital in 1889 and was president of its association for fifty years; even in the past year he had led the successful campaign to raise funds for its new building. He had been a member of the Board of Selectmen, town-meeting moderator, a member of the Board of Health, vice-president of the Clinton Trust Company and a director of the Clinton Savings Bank.

In 1894 he became a member of the Massachusetts Board of Registration in Medicine, and in 1913 its secretary. He had been a councilor of the Massachusetts Medical Society since 1898 and was president from 1912 to 1914. He was president of the Worcester District Medical Society in 1903.

In 1920 Dr. Bowers was active in effecting the purchase by the Society of the *Boston Medical and Surgical Journal*, then in an honorable but impecunious decline. He became its managing editor in the following year, thus assuming an added responsibility that necessitated his retirement from the secretaryship of the Board of Registration in 1922, a year before he would have been eligible for a pension. During his editorship, which he held until 1937, he brought the *Journal* back to a position of national prominence, fully justifying its purchase by the Society.

We all knew Dr. Bowers as an uncomprising advocate of the best type of medical practice, as a tireless worker in behalf of the Massachusetts Medical Society and as a leading medical journalist. His community knew him as a public-spirited citizen and as a skillful, devoted practitioner of medicine. A smaller circle knew him as an ardent sportsman, carrying his fishing rod with him in the spring and his gun in the fall on his long drives through his native countryside, and as the hunting companion of his old friend, the late Dr. E. Amory Codman. A few only knew of his hidden kindnesses, of the young people whom he had helped through school or college or of the aid that he had given to various younger colleagues in his profession.

In the whole conduct of his life he was the good physician, and it was as such that President Conant of Harvard University recognized him in conferring on him the honorary degree of master of arts in 1935, shortly after Dr. Bowers's eightieth birthday — "A physician devoted to his calling, for more than forty years a general practitioner in Worcester County, he has brought skill and wisdom to countless homes."

CORRESPONDENCE

INSTITUTE OF THE HISTORY OF MEDICINE

To the Editor: An editorial that appeared in the May 22, 1947, issue of the *Journal* suggests for discussion several topics that are of great interest to the medical profession of Boston and New England. The title of the editorial is "New York Academy of Medicine," and the writer points out some of the activities of the New York institution, briefly compares Boston with New York and closes with a paragraph that I quote in full, underlining three words to which I wish to call attention:

> There is, *curiously*, no similar organization in New England, although the various functions of an academy are *adequately* carried on by the state medical societies, the medical schools and, *notably*, the Boston Medical Library, fellowship in which carries with it a dignity and an intellectual prestige that still have their value.

"The various functions of an academy are *adequately* carried on by . . . *notably* the Boston Medical Library." As I understood the situation, the basis for the appeal by the Boston Medical Library to the Massachusetts Medical Society for assistance was that the services actually rendered by the Library were notably inadequate.

I quote from the Fleming report *A Factual Survey of the Medical Libraries in Boston*, dated 1941 but still pertinent, since little if any progress was made during the War. The first quotation is from the general section of this survey:

> The administration of Boston's medical libraries has not attained the general standards of library administration in evidence in the rest of the country. . . . It is noticeable that the use made of Boston medical libraries has been generally less than that commonly reported elsewhere. Although many factors enter into this apparent difference in use, it is the opinion of this observer that the basic factors are the failure of the Boston medical libraries to provide (1) adequate reading facilities, (2) expert bibliographical and reference services, (3) instruction in the use of the library, (4) ready access to the literature, (5) messenger service between library and laboratory and (6) sufficient copies of heavily used material.

Persons who use the Boston Medical Library may easily check on these points to see what is true of that institution.

I quote also from the section of the report dealing with the Boston Medical Library:

> Despite the magnificent resources which it has available, neither the support nor the use of the library has been up to expectations. [Some of the alleged trends are then noted.] If these assumptions are true, then support for the Boston Medical Library will continue to fall off, and this splendid collection, which is unexcelled in many fields and vitally essential for the practicing physician and research worker alike, will face a somewhat uncertain future . . . . This library is now faced with the serious problem of adjusting itself to new conditions. Should it remain the "gentleman's" library of the past, where tradition still is the important factor, or should it expand its services to meet the changing conditions which confront it.

The rather restrained Fleming report does not use the words "adequately" and "notably" to characterize the way in which the Boston Medical Library is carrying on its functions.

The writer of the editorial says, "There is, *curiously*, no similar organization in New England," but he does not satisfy the curiosity of the medical profession whom he is addressing. There have been, to my knowledge, in the past thirty-five years, two serious and not insignificant movements to improve greatly what may be called briefly the general set-up involving the Boston Medical Library as the center. These came to nothing and local petty jealousies were a critical factor in preventing progress. The reason there is no such institution in New England is because there are not persons enough who care enough to do enough to create it.

Few persons who have given thought to the subject are satisfied with the situation as it exists. Not only is it confused and chaotic, but the wider and deeper implications that are involved receive almost no attention. Yet the "magnificent resources of the Boston Medical Library . . . unexcelled in many fields," themselves a high tribute and a great memorial to the men in the past who loved books because "the chains of the mind are broken . . . by understanding of the past," lie there waiting for the magic touch of the historian to make them effective in leading us toward freedom.

The most striking fact about the world today is the confusion, much of it due to the rapid rate of change. To make adjustment to this new environment we need new ideas, new emphasis on and ways of using old ideas, new ways of escaping from old ideas that obstruct progress in our path toward freedom. Among the new ideas, which are sure to come, there will be many based on unrealistic thinking with the drive of emotional imbalance behind them. Some of these new ideas will be merely "old foes with a new face." They can be met, they must be met, with ideas based on realistic thinking, on a comprehensive and just evaluation of all the facts available, supported by sane and balanced emotional drives.

Medicine cannot escape from the general confusion. It is at least a little off balance, owing chiefly to the domination of the specialist, whose weakness is that he has lost perspective. This cannot be remedied by merely seeking the help of the general practitioner. What is needed is a reorientation of medicine itself in the light of the comprehensive view of the world, extensive and intensive, that is opened before us today. How can we get a truer perspective?

"History," writes Lord Acton, "is a narrative told of ourselves, the record of a life which is our own, of efforts not yet abandoned to repose, of problems that still entangle the feet and vex the hearts of men. He adds, "History compels us to fasten on abiding issues and rescues us from the temporary and the transient."

It may be objected that the history of medicine is a broken reed on which to lean: it has but a small and relatively unimportant place in the medical curriculum and little part in university education today. The reply to this objection is that a different approach is needed. Do we find in the tradition of the English-speaking peoples that the writing of history has been the monopoly of university professors? Were Gibbon and Grote and Macaulay and Lingard and Prescott and Motley and Bancroft and Lea, to name but a few, on university schedules? Perhaps it would be well for writers of the history of medicine to break away from university entanglements.

In summary, there is opportunity in Boston for further development of the sources of history, including a central reference library for all kinds of books that have to do with the healing art in any of its branches. In the interest of economy and efficiency, co-operation is desirable in every practicable way among all institutions needing medical libraries. Medical schools, hospitals and other institutions might reduce their libraries to the minimum compatible with the immediate working needs of the institution. All books not needed for the working library could be deposited in the central library. Facilities for the transportation of books are generally regarded as necessary.

A critical need is that there be developed in the central library a division of research, under the direction of a professional historian expert in research and exposition. As an integral part of the organization and so endowed that research does not have to be stopped because an additional janitor is needed, such a department has great possibilities. It might be called the Institute of the History of Medicine, if that seemed desirable. Bibliographic services are now usually rendered by well equipped libraries. In an important sense, research should be the mainspring of the activities of the library and should be carried on at all times.

There are needed adequate reading rooms and work rooms, large and small, and ample space and other facilities for the medical activities now carried on in the Boston Medical Library, such as those of the Massachusetts Medical Society and its *New England Journal of Medicine*. Perhaps others would be added later. It is clear that the present buildings of the Boston Medical Library do not lend themselves to the development of a large auditorium and rooms appropriate for smaller meetings.

What the project is called is of secondary importance. It might be planned to meet the present, and so far as can be foreseen, the future needs of the community, which includes New England, for years to come. In any case it should be an outgrowth of community conditions to meet community needs, keeping in mind always the principle of seeing the part in the light of the whole. If this principle is followed, the project might become of national importance, worthy of support by educational philanthropy.

STEPHEN RUSHMORE

520 Commonwealth Avenue
Boston

BOOK REVIEWS

Victory over Pain. A history of anesthesia. By Victor Robinson, M.D. 8°, cloth, 338 pp., with 17 illustrations and 30 plates. New York: Henry Schuman, 1946. $3.50.

Dr. Robinson has written a history in a popular narrative form of the means used for the relief of pain and the production of surgical anesthesia from the time of antiquity, when the Greeks and Romans used herbs for this purpose, to the present, when local anesthesia in its various forms is prevalent and the possibilities of curare are being investigated.

Half the volume is devoted to the discovery and development of surgical anesthesia, by ether and nitrous oxide in the United States and by chloroform in England, during the period 1832–1850. The facts relating to Long, Wells, Jackson and Morton are given in an impartial manner, and Dr. Robinson wisely refrains from taking sides in the controversy, which is still alive after a century has passed since Samuel Colt gave his exhibitions with laughing gas. The quip of Oliver Wendell Holmes that the wisest verdict in the matter "To e(i)ther" is quoted as Dr. Robinson's judgment on the merits of the case.

Samuel Colt, of Hartford, Connecticut, inventor of the famous Colt revolver, gave exhibitions on the street corners in Ware, Massachusetts, in 1832, of the effects of laughing gas, for the purpose of raising money to be used for expenses incidental to inventing his revolver. In the section on chloroform is related the story of Samuel Guthrie and the part he played in the discovery of chloroform coincidental with Soubeiran and Liebig in 1831.

The first part of the book presents a short summary of the subject in the classical, medieval and renaissance periods and the seventeenth to the early nineteenth centuries, with chapters on Humphry Davy and nitrous oxide, Henry Hill Hickman and carbon dioxide and Mesmer and mesmerism. The last part is devoted to local, regional and refrigeration anesthesia, twilight sleep and complicated modern anesthesia apparatus. The text concludes with a bibliography that is nothing more than a short reading list of books used by the author in writing his history.

The book is well published, except that some of the illustrations are not up to standard quality, and is recommended for medical-history collections.

Therapeutic Exercise. By F. H. Ewerhardt, M.D., and Gertrude F. Riddle, B.S., R.N., R.P.T. 8°, cloth, 152 pp. Philadelphia: Lea and Febiger, 1947. $2.50.

In the preface the authors state that the purpose of this manual is to provide a text for students training in physical education, occupational therapy and physical therapy. These three groups are intensely interested in the motions that normally take place in the various joints of the body. The textbooks on which they depend to obtain this knowledge are as a rule of the type that deal with elementary anatomy and physiology. A comparatively small portion of these texts is devoted to motion. Some books discuss at length muscle action or body mechanics, but such works are few and are not quite adequate. The appearance of this manual is therefore welcome.

It supplies information pertaining to joint motions; it suggests the proper exercises to preserve such functions in health and to restore them when they become subnormal or absent after disease or injury. This is carried out in detail. For example nine pages and eleven drawings are devoted to instruction in the use of the goniometer to measure angles or degrees of motion. Fourteen pages present a brief review of the plexuses of nerves in the upper and lower extremities, their normal functions, the causes, signs and symptoms of their abnormal status, the tests to be employed in the determination of the extent of their dysfunction and the methods used to restore them to normalcy. In addition to the treatment of the upper and lower extremities the book deals with abnormal conditions of the abdominal muscles and curvatures of the back, suggesting the proper remedial exercises.

Poliomyelitis and spastic diseases are each given an entire chapter; that on the former deals at length with muscle-function testing as well as muscle training, whereas the latter discusses the medical, surgical and orthopedic aspects, together with exercise, vocational, recreational and physiotherapeutic measures for the restoration and co-ordination of the natural body mechanics.

Some of the valuable information scattered throughout the book could advantageously have been tabulated in one section, serving as a source of ready reference. Thus, in the next edition the authors might consider the advisability of incorporating a table of the skeletal muscles, with their origins, insertions, nerve supplies and actions. Another omission comprises drawings, diagrams and cuts; their inclusion in coming editions will greatly add to the value of this book by making students visualize the body structures and their relations and functions.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Pye's Surgical Handicraft: A manual of surgical manipulations, minor surgery and other matters connected with the work of surgical dressers, house surgeons and practitioners. Edited by Hamilton Bailey, F.R.C.S. (Eng.), surgeon, Royal Northern Hospital, London, surgeon and urologist, County Hospital, Chatham, surgeon, Consolation Hospital, Lambeth, senior surgeon, St. Vincent's Clinic and Italian Hospital, and consulting surgeon, Metropolitan Ear, Nose and Throat Hospital, Potters Bar Hospital and Essex County Council. Fifteenth edition, fully revised. 8°, cloth, 668 pp., with 789 illustrations. Baltimore: Williams and Wilkins Company, 1947. $7.00.

This standard British manual, the joint work of forty-four authors, has been revised to bring it up to date since the publication of the previous edition in 1944. Technical procedures have been depicted pictorially, necessitating the addition of a large number of illustrations. The popularity of the manual is evidenced by the editions printed since the publication of the first edition in 1884. The volume is well published in every way and is a credit to its British printer.

A Manual of Otology, Rhinology and Laryngology. By Howard Charles Ballenger, M.D., associate professor and acting chairman, Department of Otolaryngology, Northwestern University School of Medicine, and surgeon, Department of Otolaryngology, Evanston Hospital, Evanston, Illinois. Third edition, enlarged and revised. 8°, cloth, 352 pp., with 135 illustrations and three color plates. Philadelphia: Lea and Febiger, 1947. $4.50.

This standard manual has been revised by the addition of new material and a chapter on headaches and neuralgias of the face and head. Illustrations on clinical anatomy have been added to the various sections. The text has been prepared primarily for undergraduate medical students but should prove useful to general practitioners and nurses.

Handbook of Medical Emergencies. Compiled by eight physicians who recently completed their internships, headed by Thomas B. Fitzpatrick, M.D. 16°, cloth, 106 pp. Lithoprinted. Cambridge: Harvard University Press, 1947. $2.50.

This pocket-size manual, the combined work of a committee of eight young physicians and a board of twenty-three eminent specialists in various fields of medicine, presents in complete outline form for quick reference the essential differential diagnostic points and procedures and specific and practical management of over three hundred acute medical emergencies. Included are the exact dosages, routes of administration and complications met with during the use of the various therapeutic agents. There are general chapters on penicillin, sulfonamide and parenteral therapy. Then, in order, are discussed the infectious diseases, diseases of allergy, intoxications, diseases due to physical agents and diseases of the various systems of the body. The volume is concluded with tables of equivalents of weights and measures and of normal values in blood, urine and spinal fluid, a list of abbreviations and an index. It should prove especially useful in the wards of hospitals. The presentation of some rare conditions, such as metallic, food and drug poisonings, should make it valuable to the general practitioner.

Textbook of Medicine. Edited by Sir John Conybeare, K.B.E., M.C., D.M. (Oxon.), F.R.C.P., physician to Guy's Hospital. 8°, cloth, 1170 pp., with 30 plates and 25 figures. Baltimore: Williams and Wilkins Company, 1946. (Printed in Great Britain.) $8.00.

First published in 1929, this standard British textbook, which is the joint effort of seventeen contributors, has been revised to include material accumulated since the publication of the last edition in 1945. The articles on malaria, blackwater fever, bacillary dysentery and typhus have been largely rewritten. The article on heat has been rewritten and transferred to the section on tropical diseases. There is a new article on the menopause, and those on thyrotoxicosis and diseases of the pituitary body have been revised. A section on penicillin and an appendix on aviation medicine have been added.

P-Q-R-S-T: A guide to electrocardiogram interpretation. By Joseph E. F. Riseman, M.D., associate in medicine, Harvard Medical School, instructor in medicine, Tufts College Medical School, and visiting physician, Beth Israel Hospital, Boston. Second edition. Oblong 16°, cloth, 84 pp., with 170 illustrations. New York: Macmillan Company, 1947. $3.50.

This manual, first published in 1944, has been revised and reset.

Peripheral Vascular Diseases (Angiology). By Saul S. Samuels, M.D., consulting vascular surgeon, Long Beach Hospital, New York, attending vascular surgeon, Brooklyn Hospital for the Aged, and chief, Department of Peripheral Arterial Diseases, Stuyvesant Polyclinic Hospital, New York: 8°, cloth, 85 pp., interleaved. New York: Oxford University Press, 1947. $2.50. (Oxford Medical Outline Series.)

This outline of angiology should prove useful to students and physicians, since it furnishes in a compact form the essential facts necessary to an understanding of the various diseases of the peripheral vascular system. The material is well organized. The initial chapters deal with the anatomy of the blood vessels and the autonomic nervous system, classification and symptomatology and objective signs in general, followed by the various diseases — arteriosclerosis obliterans, thromboangiitis obliterans, Raynaud's disease, embolism, varicose veins and the rarer conditions. Each disease is discussed from the viewpoints of etiology, pathology, symptomatology, objective findings and treatment. A selected list of references is attached to each chapter.

Proceedings of the Eleventh Annual Convention of the National Gastroenterological Association. 8°, paper, 187 pp., with 23 illustrations. New York: Medical Authors' Publishing Company, 1947. $2.50. Reprinted from *Review of Gastroenterology.*

This reprint makes available in one small volume the various papers on peptic ulcer, infectious hepatitis, psychosomatic medicine and gall-bladder disease read at the convention, held in New York City June 19–21, 1946.

Physiological and Psychological Factors in Sex Behavior. By S. Bernard Wortis, M.D., and others. 8°, paper, 42 pp. New York: New York Academy of Sciences, 1947. 50 cents. Reprinted from *Annals of the New York Academy of Sciences* (Vol. XLVII).

This pamphlet contains a series of five papers that were read by authorities in their fields at a conference held by the Section of Biology and the Section of Psychology of the Academy on March 1, 1946. The material is divided into two parts: animal behavior and human behavior. In the first part the animal endocrines in relation to sexual behavior and sex behavior in primates are discussed, and the knowledge to date summarized. These papers are documented with lists of pertinent references to the literature of the subject. In the second part normal and aberrant sex behavior and sex culture are considered. Alfred C. Kinseyin, discussing sex behavior in the human animal, bases his conclusions on an extensive case-history study that has been under way at Indiana University during the past eight years, and has accumulated to date over ten thousand histories obtained by first-hand interviews with persons of wide social range, of all ages and of a diversity of backgrounds. The evidence seems to point to the fact that sex practices heretofore considered abnormal are normal in the pattern of biologic behavior. The papers are well written, clear in expression and succinct. The pamphlet is well published in every way and should be in all medical and social libraries and in the private collections of all persons interested in the scientific aspects of sex behavior.

NOTICES

MASSACHUSETTS MEMORIAL HOSPITALS

The Massachusetts Memorial Hospitals have opened in their Outpatient Department on East Concord Street a Seizure Clinic to be held on Thursday afternoons at 2 o'clock. This clinic will be under the charge of Drs. Bernard Bandler and Charles Kaufman, of the Department of Psychiatry, Boston University School of Medicine. Appointments for patients wishing to attend this clinic may be made by telephone to the clinic secretary, Miss Cutter, at KENmore 9200.

AMERICAN ALLERGY FUND GRANTS-IN-AID FOR SCIENTIFIC RESEARCH

The American Allergy Fund, an organization for the advancement of medical science founded in Cleveland slightly more than a year ago, has announced that grants-in-aid for scientific research are available. The grants will be made to investigators in the biologic sciences, both medical and nonmedical, whose problems meet the requirements of the Scientific Advisory Council; preference will be given to problems with immediate relation to allergy, although investigations in physiology, biochemistry, pharmacology, immunology, genetics and other basic sciences are solicited. Grants will be made for one year in amounts not to exceed $3,500, and may be renewed from year to year if the work in progress warrants continuation.

Applications (seven copies) should be addressed to the American Allergy Fund, 525 Erie Building, Cleveland 15, Ohio (attention: Scientific Council), and should contain the following information: a statement of specific research problems and an outline of the method or methods of procedure to be followed; a description of research facilities in the institution where the investigator will employ the grant; a tentative budget; and a statement of the applicant's research record — accompanied, if possible, by publications or reprints.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, October 2

Friday, October 3
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

Monday, October 6
*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

Tuesday, October 7
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

Wednesday, October 8
*12:00 m. Grand Rounds and Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

October 3 and 4. New York Academy of Sciences. Page 348, issue of August 28.

October 6–10. American Public Health Association. Page 456, issue of March 20.

October 6–17. New York Academy of Medicine. Page 348, issue of August 28.

October 9. Practical Points in Geriatrics. Dr. Roger I. Lee. Pawtucket Association of Physicians. 8:30 p.m. Haverhill.

October–December. Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.

October 13–18. Medicolegal Conference and Seminar for Pathologists, Medical Examiners and Coroners. Page 242, issue of August 14.

October 29–31. New England Postgraduate Assembly. Copley Plaza Hotel, Boston.

November 13–15. Association of Military Surgeons. Annual Meeting. Hotel Statler, Boston.

February 6. American Board of Obstetrics and Gynecology. Page 242, issue of August 14.

April 19–23. American College of Physicians. Page xiii, issue of July 31.

May 6–8. American Association for the Study of Goiter. Page xiii, issue of July 31.

May 11–15. American Association on Mental Deficiency. Page 140, issue of July 24.

(*Notices continued on page xix*)